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Protocol

Impact of a Postintensive Care Unit Multidisciplinary Follow-up on the Quality of Life (SUIVI-REA): Protocol for a Multicenter Randomized Controlled Trial

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Abstract

Background: Critically ill patients are at risk of developing a postintensive care syndrome (PICS), which is characterized by physical, psychological, and cognitive impairments and which dramatically impacts the patient's quality of life (QoL). No intervention has been shown to improve QoL. We hypothesized that a medical, psychological, and social follow-up would improve QoL by mitigating the PICS.

Objective: This multicenter, randomized controlled trial (SUIVI-REA) aims to compare a multidisciplinary follow-up with a standard postintensive care unit (ICU) follow-up.

Methods: Patients were randomized to the control or intervention arm. In the intervention arm, multidisciplinary follow-up involved medical, psychological, and social evaluation at ICU discharge and at 3, 6, and 12 months thereafter. In the placebo group, patients were seen only at 12 months by the multidisciplinary team. Baseline characteristics at ICU discharge were collected for all patients. The primary outcome was QoL at 1 year, assessed using the Euro Quality of Life-5 dimensions (EQ5D). Secondary outcomes were mortality, cognitive, psychological, and functional status; social and professional reintegration; and the rate of rehospitalization and outpatient consultations at 1 year.

Results: The study was funded by the Ministry of Health in June 2010. It was approved by the Ethics Committee on July 8, 2011. The first and last patient were randomized on December 20, 2012, and September 1, 2017, respectively. A total of 546 patients were enrolled across 11 ICUs. At present, data management is ongoing, and all parties involved in the trial remain blinded.

Conclusions: The SUVI-REA multicenter randomized controlled trial aims to assess whether a post-ICU multidisciplinary follow-up improves QoL at 1 year.

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KEYWORDS

critical illness; Post-ICU syndrome; Mortality; cognitive impairments; cognition; quality of life; patients; intensive care; post-traumatic; post intensive care

Introduction

Background and Rationale

In the last 2 decades, mortality has significantly decreased in the intensive care unit (ICU) [1]. However, the mortality rate at 1 year after ICU discharge remains high, ranging from 10% to 30%, according to age and severity of critical illness [2-5]. In addition, ICU survivors often develop physical, psychological, and cognitive impairments, which have been grouped under the term postintensive care syndrome (PICS) [6,7]. The incidence of post-ICU complications depends on various factors, including the patient's pre-existing medical history, age, critical illness severity, as well as ICU and post-ICU care [8]. Because PICS is a dynamic process, its incidence changes according to the time of its assessment after ICU discharge. Physical disabilities are reported in about 14%-39% of patients at 1 year after ICU discharge and are mainly related to an ICU-acquired weakness [3,9-13]. Post-ICU psychological disorders include anxiety, depression, and posttraumatic stress syndrome (PTSD), which can affect from one-fifth to two-thirds of patients [3,14-18]. They result in an increased risk of suicide [19]. Concerning cognitive functions, 30%-90% of patients will complain of impaired memory, attention, concentration, and speech fluency [8,20-23]. They are more frequent in patients with pre-existing cognitive dysfunction and among those who have severe critical illness or who have developed delirium during their ICU stay [22]. PICS has a dramatic impact on a patient's post-ICU trajectory, with an increased rate of mortality and rehospitalization and decreased return to home and work; it therefore profoundly affects a patient's quality of life (QoL) [7]. Indeed, 6-month to 1-year post-ICU mortality ranges from 10% to 45%, according to age and severity and cause of critical illness [3,4,24-26]. Nearly 5%-10% of patients are readmitted to an ICU within the first year after their ICU discharge [4,27,28]. The 6-month to 1-year post-ICU QoL is significantly lower than age and sex-matched populations, with an impairment of physical, mental, and social domains [24,25,29]. QoL has been reported as being reduced by 29%-63% [30,31].

Because of its medical, social, and economic burden, PICS has been identified by the community of ICU physicians as a research priority [7]. There have been randomized controlled trials (RCTs) on post-ICU interventions, but the type of intervention, endpoints, time frame, and populations have varied.

Briefly, a rehabilitation program has been shown to improve physical [32] and psychological [4] status and increase patient satisfaction, but it has not ameliorated health-related QoL (HRQoL) [33]. A systematic review of RCTs indicated that post-ICU follow-up models focusing on psychological or medical management interventions were associated with fewer PTSD symptoms [34]. RCTs on care coordination have shown that neither a nurse-led post-ICU program in critically ill patients nor primary care physician–led follow-up in patients with sepsis was beneficial [24,35].

At the time of the design of our RCT (ie, 2010), there were a limited number of RCTs that focused on the benefit of post-ICU care coordination, but none integrated a social follow-up. Because of the interdependency of its domains, we hypothesized that a medical, psychological, and social follow-up would be more appropriate for mitigating PICS. We carried out a multicenter RCT to determine whether a post-ICU multidisciplinary follow-up would improve QoL at 1 year and would then also improve physical, psychological, cognitive, and social status and reduce mortality and medical requirements (ie, hospitalization, outpatient consultations).

Objectives

The primary objective is to assess the impact of medical, psychological, and social follow-up on death and HRQoL at 1 year after discharge from ICU.

The secondary objectives are to assess the benefit of a post-ICU follow-up on muscle strength, functional capacities, cognitive abilities, and psychological state, as well as on social and professional reintegration.

Trial Design

The SUIVI-REA trial is an open multicenter parallel group RCT comparing a program of medical, psychological, and social follow-up with standard care in patients 1 year after ICU discharge.

Methods

Study Setting

A total of 11 centers, including 9 general hospitals and 2 university hospitals, participated in this study. Factors determining center participation were a capacity to include patients, and the availability and willingness of psychologists, social workers, and physicians to implement post-ICU consultations. All participating centers had previously participated in clinical trials. Training on study procedures was provided to all participating staff members. Documents required for the study, including the study protocol and management guidelines, were available in each participating ICU.

Eligibility Criteria

Adult patients were eligible if they (1) lived in an area near the participating center; (2) had required mechanical ventilation (MV) for more than 3 days; (3) had a life expectancy greater than 1 year (defined by a McCabe score <2 and the absence of metastatic cancer); (4) were enrolled with a general practitioner; (5) were affiliated to the social health care system; and (6) had given their written informed consent. Duration of MV of at least three days was selected for patients with severe critical illness. A general practitioner was mandatory because we believe he/she should be involved in the post-ICU follow-up program. Proximity to a participating hospital was to facilitate attendance at post-ICU consultations.

Patients were excluded from the trial if they (1) had been hospitalized in an ICU in the previous year; (2) were followed for a pre-existing chronic myopathy; (3) had been admitted for serious burns, severe brain injury, suicide, or self-induced poisoning; (4) had a psychiatric disorder or dementia; (5) were under guardianship; (5) did not speak fluent French; (6) were homeless; and (7) were pregnant. These criteria were established to exclude those not benefiting from a specific follow-up and those who were unable to give their consent or to follow the post-ICU program. Patients with chronic myopathy were excluded because 1 participating center already had in place an organized, specific long-term multimodal follow-up for this condition.

All patients from one of the participating ICUs were screened for eligibility by ICU physicians before hospital discharge. The reasons for nonrandomization were collected.

Informed Consent

Written informed patient consent had to be obtained by the investigator of the participating center. A copy of the consent form was given to every patient, with the investigator retaining a copy.

As observational studies have shown that patients with delirium were at risk of developing psycho-cognitive disorders [36], we decided to remove impairment of consciousness as an exclusion criterion because a post-ICU follow-up would be beneficial for these patients. In case of impaired consciousness (ie, delirium), the investigator sought written consent from the next of kin. As soon as the patient's status allowed, written informed consent for the continuation of the research and analyses of the data was obtained. There was no additional consent for ancillary studies.

Interventions

Explanation for the Choice of Comparators

At the time of the trial design, there was no recommendation for post-ICU follow-up, in terms of both type and rate of consultations. Therefore, the comparator did not differ from the current practice and "no post-ICU follow-up" was used to control the intervention.

Intervention Description

Patients were included at time of their discharge from the ICU either to home or to another department of the same or another hospital. By convention, day 1 corresponded to the date of inclusion. The randomization was performed after the baseline assessment at the time of inclusion. The last consultation was planned at 12 months, after the simple blinded collection of the primary endpoint.

In both therapeutic groups, patients' medical, psychological, and social scores and questionnaires were assessed at the time of inclusion and at 12 months, to evaluate whether the characteristics of the 2 therapeutic groups were comparable at baseline and to determine the respective course of post-ICU discharge impairments in both groups. The scores and questionnaires were completed by the patient alone or with the help of the research assistant. If the patient was included in the control group, the test results were sealed for disclosure at the end of the study. Test results for intervention group patients were passed to the multidisciplinary team to avoid repeating the tests.

The patients from the control group had no additional post-ICU consultation. In the intervention group, patients received a multidisciplinary consultation within the first weeks after inclusion, at 3 months, and (if necessary) at 6 months. This was a consultation with a physician, a psychologist, and a social worker. Both the physician and social worker were from the ICU participating in the trial. The ICU-referring psychologist was active in 9 centers. A psychologist was specifically recruited for performing the follow-up in the remaining 2 centers. The

same multidisciplinary team was used for follow-up in each patient.

The ICU physician consultation comprised (1) the collection of information about the current treatment, weight, vital signs, comorbidities, and symptoms; (2) the date and cause of readmission at the hospital; (3) standardized general examination; (4) functional status using the Medical Research Council (MRC) sum score for assessing muscle strength and the Barthel index and Instrumental Activities of Daily Living (IADL) scores for assessing disability; and (5) cognitive status using the Minimal Mental State (MMS) scoring system. It was recommended that the participant was followed by the same ICU physician throughout follow-up. The ICU physician could prescribe a paraclinical exploration or a treatment, but it was recommended that they referred to the patient's general practitioner, except in the case of an emergency.

The consultation with the psychologist consisted of the collection of the Hospital Anxiety and Depression Scale (HADS) and Impact Event Scale-Revised (IES-R) scores for assessing PTSD as well as an interview during which the participant reported any psychological difficulties. The consultation with the social worker consisted of the collection of the social questionnaire response and an interview during which the patient reported about their QoL (Euro Quality of Life-5 dimensions [EQ5D]), social and professional difficulties, and needs.

In total, the medical, psychological, and social consultations took 2 h and 30 min. They were followed by a meeting between the ICU physician, psychologist, and social worker to discuss the participant's status and requirements and to write a summary report to forward to the general practitioner.

Criteria for Discontinuing or Modifying Allocated Interventions

Any participant could discontinue participation in the research at any time for any reason. The investigator could temporarily or permanently discontinue one's participation in the research for any reason that affected the participant's safety or was in the best interests of the participant. In the event of premature termination of the research, or withdrawal of consent, data collected prior to the premature termination could be used. The reasons for discontinuing participation in the research were to be registered in the participant's file.

Strategies to Improve Adherence to Interventions

The participating teams were informed monthly of the course of the study and reminded of the main elements of the trial. The research technician at each center organized consultations for intervention patients at 3, 6 (if needed), and 12 months. Patients were reminded of these consultations 15 days beforehand. Control patients were called at least once by the research technician to remind them of their 12-month consultation, which was planned at time of their ICU discharge.

Relevant Concomitant Care Permitted or Prohibited During the Trial

For deontological reasons, the patients of both groups continued to be followed by their general practitioner or specialist physician, but they were allowed to see a new physician, a physiotherapist, or psychologist. The purpose of the trial was to determine whether a post-ICU follow-up improved standard patient care.

Provisions for Posttrial Care

In France, the research sponsor insurance offers a subsequent period of insurance 10 years from the end of the research. Consequently, in the event of poststudy damage to participants related to their participation in the research, the complaint would be admissible whenever it occurred during this period.

Outcomes

The primary outcome was QoL at 12 months. The QoL was assessed using the EQ5D and by telephone by a blinded investigator. The patient was asked not to disclose to which group they were randomized. The EQ5D is a standardized self-completed instrument for measuring generic HRQoL. The Euro Quality of Life-5 dimensions-5 Levels (EQ5D-5L) comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 problem levels: none, slight, moderate, severe, and extreme. Finally, the weighted sum of the responses obtained provides a cardinal measure (between 0 for death and 100 for the total absence of a problem), which is also suitable for medicoeconomic evaluation [37]. The EQ5D has been used in various post-ICU follow-up studies [30,35,38-41]. The secondary outcomes were mortality, cognitive, psychological, and functional status; social and professional reintegration at 1 year; as well as the rate of rehospitalization and outpatient consultations within the first year (Table 1).

Table 1. Research timeline for each participant.

Timepoint	Inclusion	ICU[a] discharge	3 months	6 months	12 months
Consent collection	Both groups				
Pursue consent collection		Both groups	Both groups	Both groups	
Demographics, medical history, critical illness, and ICU stay characteristics	Both groups				
Collection of clinical data	Both groups	Follow-up group	Follow-up	Follow-up	Both groups
Standard biological tests	Both groups		group	group	Both groups
Adverse events		Follow-up group	Follow-up	Follow-up	Both groups
Final assessment of main outcome					Both groups
Final assessment of secondary outcomes					Both groups

[a]ICU: intensive care unit.

Sample Size

At the time of the study design, other studies indicated that 10% of patients discharged from ICU died within the first year and 40% had a moderate to severe impairment on at least one dimension of the EQ5D [32,41].

Therefore, we estimated that at least 50% had a very poor outcome, combining death and severe to extreme impairment of at least one EQ5D dimension. [23]. The study was then powered to detect a decrease from 50% to 37% of patients with very unfavorable outcome with a power of 80% and a 2-sided 5% alpha risk, assuming this rate would be 50% in the control arm. Accordingly, the sample size was 249 patients per group. We anticipated that 20% of the patients would be lost to follow-up, so the sample size was increased to 300 per arm. The study therefore initially planned to enroll a maximal sample size of 600 patients. However, as the rate of loss to follow-up has, indeed, proved to be 10%, we decided to decrease the sample size to 520 patients. Finally, 546 patients were included.

Interestingly, recent studies on comparable populations of critically ill patients showed that there was a 1-year mortality rate of between 10% and 28% [2,3,5,8,20] and that about 60% of patients had a moderate to severe impairment on at least one dimension of the EQ5D [3,10,29]. These findings suggest that our original estimation is still appropriate.

Recruitment

The study took place in 11 ICUs, which had been selected based on the interest expressed by local teams in post-ICU follow-up, for their capacity to recruit patients and to handle the restraints of an RCT. A research assistant was available at every participating center to screen patients for inclusion. The steering committee met monthly. A centralized phone and email center answered participating center questions regarding patient eligibility or management during the entire trial period. A monthly newsletter was circulated, informing participating centers of the number of patients included, main study constraints, and any protocol modifications (Table 2).

Table 2. Number of patients included and participating centers and inclusion rate.

Evaluation	Values required
Number of patients to be included	546
Number of centers	11
Number of months	54
Number of patients per month per center	1

Assignment of Interventions: Allocation

Sequence Generation

The randomization list, generated by an independent statistician, was balanced between arms. Randomization was stratified by center using a permuted block of unrevealed size randomization. As critical severity could potentially impact the rate and intensity of psychological, cognitive, and physical impairment, stratification was made on this basis.

Concealment Mechanism

Randomization and concealment were ensured by using a secure dedicated web-based system accessible at each study center and managed by the clinical research unit (CRU), which had no role in patient recruitment.

Implementation

The allocation sequence was generated by the study statistician. Patient enrollment was established by the participating center investigator.

Assignment of Interventions and Blinding

The outcome assessor assessing the EQ5D by phone was blinded. Neither the participants nor the investigators (ie, ICU physicians, psychologists, and social workers) were blinded for patient assignment to one of the trial groups. The procedure for

unblinding was not planned as the intervention was considered safe.

Data Collection and Management

Plans for Assessment and Collection of Outcomes

At inclusion, baseline characteristics were systematically collected by the center investigator as follows: demographic and anthropometric data; location prior to ICU admission (community, hospital, or long-term facility); pre-existing comorbidities using Knaus, McCabe, and Charlson scores; date and time of ICU admission; and severity of critical illness at ICU admission using the Simplified Acute Physiology Score (SAPS-II) and the Sequential Organ Failure Assessment (SOFA) score [42,43]. In addition, body weight, height, vital signs, MRC sum score [9], the Barthel index [44], IADL scores [45], MMS [46], HAD-S [47], IES-R [48], and the social questionnaire were collected for all participants. Patients' were also asked to score their QoL 3 months before ICU admission, using the EQ5D tool. The functional and psychological scores were completed by the patients, with help from the research technician. The MRC sum score and MMS were assessed by the ICU physician in charge of the patients. This assessment ensured that both the functional, cognitive, psychological, and social status and pre-ICU QoL were comparable between the 2 trial groups. Finally, blood samples were taken for standard biological tests, including blood cell count; biochemistry; and plasma levels of C-reactive protein, pre-albumin, albumin, and thyroid hormones.

At time of ICU discharge the duration of MV, need for tracheostomy, and length of ICU stay were also recorded.

Intervention group patients were seen by the ICU physician, the psychologist, and the social worker before ICU discharge (month 0) and at 3 months, and eventually at 6 months by the follow-up team. The psychologist and social worker had access to the scores and questionnaire completed by the patients at inclusion. At 3 and 6 months, the MRC sum score, Barthel index, IADL, MMS, HADS, and IES-R were collected as well as the social questionnaire and results of the biological tests.

At 12 months, the EQ5D (ie, primary endpoint) was assessed on the phone by a blinded assessor. All patients were seen by the ICU physician, psychologist, and social worker. The MRC sum score, Barthel index, IADL, MMS, HADS, and IES-R, together with the 36-item Short Form (SF-36) for assessing QoL and the social questionnaire, were collected. Standard biological tests were performed at 12 months.

The reason for failure to attend the planned consultation was recorded by the research technician via telephone. The date and cause of readmission to hospital and death were also documented. The number of consultations with the general practitioner or any other specialist was recorded.

Plans to Promote Participant Retention and Complete Follow-up

Each month, the participating teams were informed of the course of the study and reminded of the main elements of the trial, notably concerning the organization of the follow-up consultation.

Data Management

Data management and statistical analysis were performed independently of the sponsor and of investigators by the CRU (Unité de Recherche Clinique, Hôpital Ambroise-Paré, Boulogne-Billancourt, France). Data entry was performed by the investigator at enrolling sites using a web-based data entry system.

An electronic case report form (eCRF) was developed by the CRU using dedicated software (CleanWeb) to facilitate data control and monitoring. Each patient was assigned a unique study ID that was used to index the eCRF and related study documents. It captured data from each included patient.

All information required by the protocol had to be entered in the eCRFs. Data were recorded in the eCRF as and when they were obtained. Any missing data had to be coded. In-built consistency checks instantly verified the coherence of data.

Data monitoring was performed by the sponsor (Direction de la Recherche Clinique et de l'Innovation de l'Assistance Publique – Hôpitaux de Paris [DRCI AP-HP]). This project was classified as interventional with potential risks based on the AP-HP risk level classification, meaning that a high level of monitoring is necessary for determining whether centers adhere to the protocol and procedures, for checking for eCRF completeness, for ensuring patient safety (adverse event/serious adverse event), and for follow-up in accordance with the applicable regulations. A clinical research associate (CRA) appointed by the sponsor is responsible for timely completion of the study and for collecting, documenting, recording, and reporting all handwritten data, in accordance with the standard operating procedures applied within the DRCI APHP and in accordance with Good Clinical Practices as well as the statutory and regulatory requirements. During these visits, the following elements were reviewed:

- Written consent.
- Safety and rights of participants being protected.
- Compliance with the study protocol and with the procedures defined therein.
- Quality of data collected in the eCRF (accuracy, missing data, consistency of the data with the "source" documents, such as medical files, appointment books, original copies of laboratory results, etc.).
- Data were authentic, accurate, and complete.

The CRA systematically checked baseline characteristics, eligibility criteria, primary outcome, and serious adverse events reported in the eCRF for all study participants. In addition, for one-third of the study population, all data reported in the eCRF were validated against a patient's original chart. Serious adverse events and major protocol violations were reported to the DRCI APHP and Comité de protection des personnes (CPP; Ethics Committee).

At the end of the study, after clarification of discrepancies (data cleaning) and data validation, the database was frozen and transmitted to the statistician, following procedures established by the sponsor.

Each patient participated in the trial for 12 months. Premature study withdrawal was at the request of the patient or next of kin and their reasons were recorded in the eCRF and the patient's medical file. Withdrawn patients were not replaced. However, patients who were lost to follow-up or did not receive the randomly assigned treatment were not considered to be prematurely withdrawn from the trial.

Confidentiality

As for any clinical research supported by the AP-HP, processing of personal data complied with the methodological requirements for a clinical trial established by the French Data Protection Authority Commission Nationale de l'Informatique et des libertés Commission Nationale de l'Informatique et des libertés (CNIL) in January 2006 for biomedical research. During and after the clinical research, all collected data sent to the sponsor by the investigators (or any other specialized collaborators) were pseudonymized using only the participant's initials. Under no circumstances the names and addresses of the participants involved had been shown. Only the participant's initials and an encoded number specific to the study indicating the order of enrollment were recorded. Moreover, all nominal data were erased on the copies of the source files that were used for research documentation.

Plans for Collection, Laboratory Evaluation, and Storage of Biological Specimens for Genetic or Molecular Analysis in This Trial/Future Use

No genetic or molecular analyses were planned.

Statistical Methods

Statistical Methods for Primary and Secondary Outcomes

The 1-year survival rate without major deterioration in QoL (main endpoint, defined as reporting of death or a severe to extreme problem" level in 1 of the 5 dimensions studied) will be compared between both arms using a piecewise exponential model considering any censorship and the repeated nature of observations, prohibiting the use of conventional methods of analysis of censored data. This analysis will be adjusted for age and severity of critical illness (according to SOFA grading), and the center will be considered as a random effect. In addition, 2 analyses will be performed, according to age category (with cut-off at 65 years) and severity of critical illness (with a cut-off at the median value).

Binary outcomes will be analyzed using logistic regression. Absolute risk reductions will be obtained using a binomial model with identity link [49]. For time-to-event outcomes, Kaplan-Meier survival curves or cumulative incidence curves will be estimated, and the intervention effect will be analyzed using the Cox proportional hazards regression. Mixed linear regression will be used for continuous outcomes, possibly after variance-stabilizing transformation. All tests will be 2-sided at a .05 significance level.

Interim Analyses

We neither planned nor performed an interim analysis.

Methods for Additional Analyses (eg, Subgroup Analyses)

Age and severity of critical illness as predictors of poor outcomes and practice might differ between centers, so randomization was stratified by center and statistical analysis is adjusted for these factors to minimize discrepancies between therapeutic groups.

Methods in Analysis to Handle Protocol Nonadherence and Any Statistical Methods to Handle Missing Data

Intent-to-treat statistical analysis will be performed after all patients have completed the 1-year follow-up. Accordingly, all patients will be analyzed in the arm they were allocated to, regardless of protocol deviations. In addition, missing outcome data will be imputed. Prior to any data analysis, a detailed statistical analysis plan will be drawn up by the study statistician. There will be a comprehensive report of the statistical analysis, following the CONSORT statement recommendations. Any change in the analysis plan will be justified in this final report.

While no missing data are expected, the maximum bias method will be used for analysis of the primary outcome, replacing missing data by a success in the control arm and by a failure in the intervention arm. For secondary outcomes, missing data will be handled by multiple imputations by chained equations. A sensitivity analysis of complete cases only will be performed.

Plans to Give Access to the Full Protocol, Participant-Level Data, and Statistical Code

Those with direct access in accordance with the laws and regulations in force, in particular articles L.1121-3 and R.5121-13 of the Public Health Code (eg, investigators, those responsible for quality control, monitors, CRAs, auditors, and others involved in collaborating on trials), will take all necessary precautions to ensure the confidentiality of information relating to the tested drugs, the trial, and the trial participants, especially with regard to their identity and the results obtained. The data thus collected during quality controls or audits are then made anonymous.

Oversight and Monitoring

Composition of the Coordinating Center and Trial Steering Committee

The steering committee is composed of DF and TS who initiated the project, the methodologist and the sponsor's representatives (DRCI and CRU APHP) appointed for this research. The steering committee aimed at deciding during the trial the procedures to be followed, taking note of the recommendations of the independent supervisory committee. It defined the general organization and conduct of the research, and coordinated the information. It also decided the appropriate methodology to conduct for unforeseen circumstances. During the trial period it will determine and monitor the progress of the research, particularly in terms of tolerance and adverse events.

Composition of the Data Monitoring Committee, Its Role, and Reporting Structure

There was no Data Safety Monitoring Board (DSMB) as the intervention was considered safe for the patient.

Adverse Event Reporting and Harms

Any adverse event occurring during the trial period was reported by participating centers via a centralized phone and email system. Serious adverse events and major protocol violations were reported to the DRCI and CPP.

Plans for Communicating Important Protocol Amendments to Relevant Parties (eg, Trial Participants, Ethical Committees)

All substantial modifications to the protocol by the coordinating investigator were sent to the sponsor for approval. After approval was given, the sponsor obtained approval from the CPP (Research Ethics Committee) and authorization from the Agence Nationale de Sécurité du Médicament (ANSM) within the scope of their respective authorities before the amendment was implemented.

The information note and the consent form had been revised, particularly in case of a substantial amendment to the study.

Dissemination Plans

Neither the study sponsor nor the study funder had any role in designing the trial, managing, analyzing, or interpreting the data, writing the report, or in the decision to submit the report for publication.

Patient and Public Involvement

No patient involved.

Availability of Data and Materials

In accordance with Good Clinical Practice: (1) the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents, and the reports, for the purposes of the sponsor's quality control and audit procedures or inspections by the competent authority; (2) the investigators allow individuals in charge of monitoring and quality control to have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code).

The AP-HP had full access to patients' charts and checked all data recorded in the eCRF against original charts. All information required by the protocol had to be provided in the electronic logbook and an explanation given by the investigator for any missing data.

Ethics Approval and Consent to Participate

Methodological aspects were independently approved by the national jury of the Clinical Research Hospital Program in 2010, and the Ministry of Health confirmed funding under contract number AOM10072. The protocol and qualification of all investigators were approved by the CPP of Saint-Germain-en-Laye, France, on July 08, 2011. The CPP allowed for waiver of consent and deferred consent (number 11052). The trial was registered at Clinicaltrials.gov identifier NCT01796509 (registered on February 21, 2013).

Written informed consent of the patient had to be obtained by the investigator of the participating center. In case of impaired consciousness, the investigator sought for written consent from the next of kin. If the latter was not present, the patient could be included as deferred consent, as has been approved by the Ethics Committee, according to French law (Art L1122-1-2 du Code de la Santé Publique). As soon as the patient's status allowed, written informed consent for the continuation of the research and analyses of the data was obtained. A copy of the consent form was given to every patient. The original copy must be retained in the investigator's archive for a minimum of 15 years. A third copy is archived by the sponsor. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

The study was funded by the Ministry of Health in June 2010. It was approved by the Ethics Committee on July 8, 2011. The first and last patient were randomized on December 20, 2012, and September 1, 2017, respectively. A total of 546 patients were enrolled across 11 ICUs. At present, data management is ongoing, and all parties involved in the trial remain blinded.

The first patient was recruited on December 20, 2012, and the last patient on September 1, 2017. The study was never suspended. The assessor of the primary endpoint and study statistician remained blinded to study intervention throughout the trial. Data management is ongoing. Release of the results is planned for end of 2022.

There were 10 amendments to study protocol (Multimedia Appendix 1). All amendments were approved by investigators, study statistician, AP-HP, CPP, and ANSM.

The DRRC organized data monitoring and quality audits. Baseline characteristics, eligibility criteria, primary outcome, secondary outcomes, and serious adverse events reported in the eCRF were systematically checked against original charts for all research participants. In addition, for one-third of the study population, all data reported in the eCRF were validated against a patient's original chart. Serious adverse events and major protocol violations were reported to the DRRC, ANSM, and CPP. The study coordinator had quarterly face-to-face meetings with the DRRC and AP-HP to monitor trial conduct according to the highest standard for protection of research participants. All randomized patients completed follow-up for the primary outcome.

Monitoring of the data has been completed. Freezing of the database and statistical analysis are planned within the next 6 months.

Discussion

Overview

PICS is a major public health issue, affecting more than half of critically ill patients 1 year after their discharge from an ICU [8]. It has a huge impact on QoL, affecting a patient's personal, social, and professional life. In their Cochrane review, Schofield-Robinson et al [50] concluded that there was "insufficient evidence, from a limited number of studies, to determine whether ICU follow-up services are effective in

identifying and addressing the unmet health needs of ICU survivors" and called for future studies that are "designed with robust methods (for example, randomized studies are preferable) and consider only one variable (the follow-up service) compared to standard care." Our trial is in line with these recommendations as it is a multicenter parallel group RCT that was designed to determine whether a medical, psychological, and social follow-up improves QoL of the critically ill patient at 1 year after ICU discharge. This hypothesis was based on the fact that PICS is characterized by interdependent elements, which would be better targeted using a multidisciplinary approach. The SUIVI-REA trial is still original and relevant. Because the use of MV at a minimum of 3 days is an inclusion criterion enabling the selection of patients with severe critical illness, the results will be obtained from a representative population at risk of developing PICS. Its results could be then compared with those of ongoing trials assessing the benefit of telehealth [51], combined physical and cognitive training [52], or multidisciplinary personalized follow-up [53].

As cognitive impairment was not comprehensively assessed, it could be argued that it was not therefore managed. In 2010, when the study was designed, post-ICU cognitive dysfunctions were not identified as a major component of PICS. Moreover, we considered that compliance would have been reduced, as a cognitive assessment would have increased the length of the consultation period and the number of questionnaires patients had to complete. In our RCT, cognitive impairment was assessed using the MMS examination, which has been validated for detecting dementia and used in cohort studies of critically ill patients [20].

The program might be thought to be an assessment of physical, psychological, and social domains rather than one of multidisciplinary care. However, we felt that the multidisciplinary teams should not replace the physicians who routinely care for a patient but rather that they should contribute to patient care, notably by detecting ICU-related complications and suggesting specific management to the patient's own doctor. Multidisciplinary teams were highly recommended to respect these deontological principles. For this reason, a concluding letter was systematically sent to the general practitioner, recapitulating the observations and propositions made by the multidisciplinary team. The impact of our intervention would therefore depend on the commitment of the multidisciplinary teams to participate in the patient's overall care. Should our intervention not have added value to routine care, our hypothesis is that its main benefit would be the expertise of the multidisciplinary team to assess and treat ICU-related complications. In addition, the social assessment would help to personalize a patient's care.

Randomization Procedure

Selection biases were minimized and randomization ensured homogeneity between the 2 groups. First, the random list for allocating interventions was computer generated by an independent statistician. Randomization was centralized through a secured website using permutation blocks, the size of which was unknown to research participants. Neither the investigators nor the patients could be blinded for the intervention. It is not possible to anticipate any advantages for an intervention and what their extent might be.

Strategies have been established for limiting the loss of follow-up and to improve patient attendance at consultations, by regular telephone reminders, planning of the consultation with the patient, and organization of the patient's home-hospital transport. Finally, amendments made to the protocol aimed to improve patient recruitment.

We neither planned nor performed an interim analysis.

Endpoints

The primary endpoint is QoL, to be evaluated using a validated scale (ie, EQ5D). We considered QoL to be the most appropriate endpoint for evaluating both a multidimensional condition (ie, PICS) and the intervention. The EQ5D has been collected by phone by an assessor blinded to randomization. This has been a customary procedure in various clinical trials evaluating QoL as the primary endpoint [29]. The secondary endpoints are conventional and will enable us to assess the impact of the multidisciplinary follow-up on the principal dimensions of PICS.

Strength and Limitations of the Study

- This is the first multicenter RCT that assesses whether a post-ICU multidisciplinary follow-up program based on medical, psychological, and social assessment will improve the QoL at 1 year.
- This RCT has been designed and powered for addressing this major issue, because ICU stay is associated with increased mortality and morbidity.
- The trial is based on a clinically relevant primary endpoint, that is, QoL, that considers mortality as well as ICU-induced physical, psychological, and social impairment(s).
- This trial concerns only adult patients discharged from an ICU.
- Because medical, psychological, and social assessments are time-consuming, a comprehensive neurocognitive evaluation was not feasible.
- Strategies were applied for limiting the loss to follow-up and improving assiduity for follow-up consultations.

Conclusion

Post-ICU interventions have been little studied and to date none have been shown to be beneficial. Therefore, SUIVI-REA is designed to demonstrate the benefit of post-ICU follow-up services for mitigating PICS in a representative population of ICU-discharged patients at risk of developing PICS. By integrating adjustments to the main outcome predictors and collecting potential confounding factors, the trial will also provide original, reliable, and relevant data on the epidemiology of PICS. This will not only help in the design of further clinical trials but also enable the development of algorithms for predicting PICS [54].

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Authors' Contributions

TS and DF conceived the study. TS, DF, LG, AM, and PA each made substantial contributions to study design, have been involved in drafting the manuscript and revising it critically for intellectual content, and have given final approval of the version to be published. PA and LG provided statistical input and contributed to the study design. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplementary table: Amendments to study protocol.
[DOCX File , 29 KB - resprot_v11i5e30496_app1.docx]

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Abbreviations

ANSM: Agence Nationale de Sécurité du Médicament
AP-HP: Assistance Publique – Hôpitaux de Paris
CNIL: Commission Nationale de l'Informatique et des libertés Commission Nationale de l'Informatique et des libertés
CPP: Comité de protection des personnes (Ethics Committee)
CRA: clinical research associate
CRU: clinical research unit
DRCI: Direction de la Recherche Clinique et de l'Innovation
DSMB: Data Safety Monitoring Board
eCRF: electronic case report form
EQ5D: Euro Quality of Life-5 dimensions
HADS: Hospital Anxiety and Depression Scale
HRQoL: health-related quality of life
IADL: Instrumental Activities of Daily Living
ICU: intensive care unit
IES-R: Impact Event Scale-Revised
MMS: Minimal Mental State

MRC: Medical Research Council
MV: mechanical ventilation
PICS: postintensive care syndrome
PTSD: posttraumatic stress syndrome
QoL: quality of life
RCT: randomized controlled trial
SAPS-II: Simplified Acute Physiology Score
SF-36: 36-item Short Form
SOFA: Sequential Organ Failure Assessment

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Protocol

Web-Based Technologies to Support Carers of People Living With Dementia: Protocol for a Mixed Methods Stepped-Wedge Cluster Randomized Controlled Trial

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Abstract

Background: Informal carers play a significant role in supporting people living with dementia; however, carers in rural areas are often isolated, with limited access to support services. Although dementia-friendly communities provide valued support for carers, access to them is limited as they are few and geographically dispersed.

Objective: This study's aim was to increase support and services for rural informal carers of people living with dementia by using information and communication technologies accessed through an integrated website and mobile app—the Verily Connect app. The objective of this protocol is to detail the research design used in a complex study that was situated in a challenging real-world setting integrating web-based and on-ground technology and communication. Therefore, it is anticipated that this protocol will strengthen the research of others exploring similar complex concepts.

Methods: A stepped-wedge, open-cohort cluster randomized controlled trial was conducted to implement Verily Connect across 12 rural Australian communities. The Verily Connect intervention delivered web-based, curated information about dementia, a localized directory of dementia services and support, group and individual chat forums, and peer support through videoconference. During the implementation phase of 32 weeks, Verily Connect was progressively implemented in four 8-weekly waves of 3 communities per wave. Usual care, used as a comparator, was available to carers throughout the study period. Participants and researchers were unblinded to the intervention. There were 3 cohorts of participants: carers, volunteers, and staff; participants were recruited from their communities. The primary outcome measure was perceived carer social support measured using the Medical Outcomes Study-Social Support Survey. Volunteers and staff provided feedback on their participation in Verily Connect as qualitative data. Qualitative data were collected from all cohorts of participants through interviews and focus groups. Process

evaluation data were collected through interviews and memos written by research staff. Data on the costs of implementing Verily Connect were collected by the research team members and evaluated by a health economist.

Results: Between August 2018 and September 2019, a total of 113 participants were recruited. There were 37 (32.7%) carers, 39 (34.5%) volunteers, and 37 (32.7%) health service staff. The study was complex because of the involvement of multiple and varied communities of carers, volunteers, health service staff, and research team members originating from 5 universities. Web-based technologies were used as intervention strategies to support carers and facilitate the process of undertaking the study.

Conclusions: The Verily Connect trial enabled the testing and further development of a web-based approach to increasing support for carers of people living with dementia across a diverse rural landscape in Australia. This protocol provides an example of how to conduct a pragmatic evaluation of a complex and co-designed intervention involving multiple stakeholders.

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KEYWORDS

virtual; dementia; community; rural; carer; caregiver; mobile phone

Introduction

Background

Approximately 50 million people live with dementia worldwide [1], including an estimated 470,000 Australians [2]. Much of the care given to people living with dementia is provided by informal carers, including family, friends, and neighbors, who do so without financial remuneration [3,4]. Although caring is frequently motivated by love and concern, caring for someone with dementia can also be burdensome and is linked with the added risk of social isolation [5-7] and carer distress [8]. Those who care for a person living with dementia tend to have less time for holidays, leisure activities, and family and friends [9]. As a group, carers are more likely to have smaller social networks than people without caring responsibilities, and social support can often decrease over time [7,10]. Although informal carers are at risk of social isolation, when social support is available, social isolation is reduced [7], which points to the need to find ways to increase formal and informal social support for carers.

The health of people living in rural and remote areas of Australia is noted to be poorer than that of people living in metropolitan areas, and access to health services is also reduced in rural and remote areas [11]. In rural areas, obtaining support for informal carers of people living with dementia is very challenging as rural people must often travel long distances to access specialist services [12]. In addition, rural dementia service users, carers, and providers report challenges and vexation when trying to locate appropriate services within a fragmented health system [13]. Dementia often attracts social stigma [14] and, in small rural communities in which residents are familiar with each other, carers of people living with dementia may avoid seeking support to maintain their privacy.

Although the peak organization for providing dementia information and support in Australia, Dementia Australia, provides a range of resources for people living with dementia and carers, there remain challenges for rural Australians in accessing resources relevant to their local area context [15]. For example, some services (such as carer support groups and dementia cafés) are not available in most rural communities. The Dementia Friendly Community movement, which aims to help members of communities better understand dementia and be aware of and accept people living with dementia in their community [16], helps address challenges in supporting rural carers. However, the support provided is solely for communities that have invested in becoming a dementia-friendly community. Thus, access to this support can be patchy. For rural people, the challenge is not lack of existence of services and support per se but rather that programs are provided distant from where rural people live [15].

The Verily Connect study was built on the hypothesis that information and communication technologies (ICTs) could be leveraged to provide increased support and services to rural carers of people living with dementia. (The study is named as a loose acronym for Virtual Dementia-Friendly Rural Community.) Using technology, rural carers might be assisted to identify, contact, and find their way to the services and support they need using easily accessible and locally relevant information anytime and on demand provided by the specially designed Verily Connect app. Along with the app, the use of videoconferencing to facilitate peer support and information sharing between carers was an additional feature designed to help reduce the need to travel to access support. Videoconferencing support groups for carers of people living with dementia have been demonstrated to reduce caregiver distress, depression, and feelings of loneliness [17]. The Verily Connect project was hypothesized to provide a way to build a web-based dementia-friendly community that would also be connected to and support on-the-ground dementia-friendly communities. Provision of support on the web (through information and web-based peer support) was proposed to augment the support available to the on-the-ground communities in an efficient and cost-effective way and thus assist with scaling up the spread of on-the-ground dementia-friendly rural communities.

Prior Work

Although there has been significant uptake in work using web-based technologies to support carers of people living with dementia within the last 5 years (and especially in response to COVID-19 pandemic social distancing restrictions), the idea

was novel in 2016, when the Verily Connect study was pitched for funding. A systematic review of studies using web-based technology to support informal carers of people living with dementia identified only 3 relevant studies in the period of 1990 to 2012 [18]. In 2013, Godwin et al [18] concluded that, although feasibility studies had shown promising results for using web-based technology to reduce the burden experienced by informal carers, more randomized controlled trials were needed to evaluate these interventions. Another systematic review of internet-based supportive interventions for carers of people living with dementia conducted in 2014 concluded that, although interventions that combined information and opportunities for peer interaction showed the most potential, more research on these types of interventions was needed [19]. Several studies evaluating the use of web-based technology to support carers of people living with dementia were commenced in 2016 to 2017 [20-22].

The Verily Connect project was designed to build on and extend the previous work of project investigators and other researchers. In 2016, a study was completed in rural communities in Australia to identify gaps in service provision and support for people living with dementia and their carers [23]. This research found that carers of people living with dementia in the community would benefit from learning about services that were available in their local geographical area and how they could access these services; having someone to talk with and the opportunity to receive respite were also reported as service gaps [23]. A finding of the study was that local service delivery might be improved by training volunteers to work in an integrated way with health care providers to assist and support carers [23].

On the basis of the project findings, a prototype smartphone app for helping carers of people living with dementia navigate health and aged care services and increasing support and connection between carers and service providers was piloted in 2016 with 2 rural communities. The Service Navigation and Networking for Dementia in Rural Communities app was co-designed and coproduced with rural carers, service providers, and other stakeholder representatives (including Alzheimer's Australia Victoria) [24]. Feedback from the pilot indicated that more flexible support from services was needed and that carers (most of whom were older people) needed assistance in developing confidence in using web-based technologies.

The videoconferencing aspect of this study was based on the work of O'Connell et al [25] in rural Canada. That study demonstrated that support groups conducted by videoconference were able to increase support for people living with dementia and their carers. This type of technology-enabled service was advantageous for the rural participants as it reduced the need to travel long distances in sometimes treacherous weather and road conditions to access the needed support.

Goal of the Study

The Virtual Dementia-Friendly Rural Communities (Verily Connect) project aimed to develop, trial, and evaluate a web-based intervention for increasing support for informal carers of people living with dementia in rural communities. The main objective was to determine whether support perceived by carers, as measured by the Medical Outcomes Study-Social Support Survey (MOS-SSS), increased after the implementation of the Verily Connect intervention.

A secondary objective was gaining feedback about the usability and usefulness of Verily Connect. Another secondary objective was to evaluate the process of implementing Verily Connect to better understand the barriers to and enablers of its implementation and to complete a cost analysis of implementing Verily Connect.

Methods

Study Design

A stepped-wedge, open-cohort cluster randomized controlled trial design [26,27] was used to trial the implementation of Verily Connect across 12 rural Australian communities. The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12618001213235). Each cluster comprised 1 geographically defined rural community. During the control period, the participants had access to their usual care. During the implementation period (32 weeks in total), Verily Connect was progressively implemented in each of the 12 participating rural communities across 4 periods of 8 weeks each. (Each 8-week period was considered a *wave*.) In each wave, 3 clusters moved from the control phase to the implementation phase. Thus, at 8-weekly intervals, 3 additional clusters (ie, 3 rural communities) received the Verily Connect implementation. Multimedia Appendix 1 provides a diagram of the stepped-wedge control and implementation periods.

Each cluster experienced a control phase and an intervention phase. However, the length of the control and intervention phases differed for each cluster. Some clusters commenced the intervention earlier and had a longer exposure than clusters that commenced later. A staggered start date for different clusters was pragmatic; start-up activities such as volunteer training and onboarding of participants to use the technology were significant and, therefore, each wave needed an 8-week implementation cycle. However, owing to funding requirements, the entire project (from ethics application to final reporting) needed to be fully executed within 3 years. The implementation phase commenced in August 2018 and concluded in March 2019.

Ethics Approval

The study received approval from the Melbourne Health Human Research Ethics Committee (application HREC/17/MH/404, reference 2017.376) after being assessed as meeting the requirements of the Australian National Statement on Ethical Conduct in Human Research (2007) and of the Helsinki Declaration of 1975, as revised in 2000.

Intervention

There were 3 main components of the Verily Connect intervention. Two of these components were web-based, and the third was designed to provide carer participants with additional support in using the web-based components. The 3 components are outlined in Textbox 1.

Textbox 1. The 3 main components of the Verily Connect intervention.

Intervention components

1. An integrated website and mobile app (Verily Connect app). The Verily Connect app had 2 main functions: information provision and facilitation of social communication between users. General information relevant to a carer of a person living with dementia was provided by 12 *guides*. The guides were developed by the research team; they were deliberately brief and curated from freely accessible but reputable internet sources. Links to information sources were accessible on the app and could be clicked to open the linked source in a web browser. For each participating community, there was a directory of locally available dementia-relevant services that were geographically displayed using Google Maps. Service information included links within the app that directly connected app users to the telephone, email, Facebook, and website of the listed service (where available). In addition, the Verily Connect app provided opportunities for app users to connect with each other using a text-based chat function presented as *forums*. During the trial, to control when communities had access to the Verily Connect intervention, access to the Verily Connect app was password-protected; the research team gave participants access to a password and the app when their community entered the intervention phase.
2. Carer peer support groups that met via Zoom (Zoom Video Communications) videoconference. The project manager facilitated the implementation of the support groups by providing technical assistance and information about the group and videoconference etiquette (including precautions about privacy, confidentiality, and being secure when using the internet), making introductions, and ensuring that all members were given the opportunity to contribute to discussions. Most groups did not have a specific agenda; rather, the participants could speak about whatever they wanted. The project manager used minimal questioning and prompting to encourage conversation and ensure that every participant had a turn to speak. A challenge sometimes arose if a participant had poor internet connectivity and, therefore, had trouble keeping up with the group conversation. Another challenge arose when only one of the group members joined by telephone while the others were on videoconference; the person on the telephone missed nonverbal cues provided by those on videoconference and, consequently, there were some miscommunications and frustration with mistiming of discussions. The first carer peer support group was held at the end of wave 2 as this length of time was needed for sufficient carers to be recruited and their communities to enter the intervention phase. Thereafter, the carer peer support groups met monthly. Attendance at carer peer support groups was managed by direct invitation to participants whose communities had entered the intervention phase.
3. Volunteer support and a *Technology Learning Centre* (also known as a Verily Connect Hub) that was physically located in each community. The role of the volunteers was to assist carers and other interested community members in learning how to use the Verily Connect app and other relevant web-based technologies (such as Zoom videoconferencing). Volunteers were governed by a health service or volunteer organization in their local community, and they received a day's training from Verily Connect project staff. The Verily Connect project also facilitated support for volunteers via group videoconference meetings. Verily Connect Hubs were slightly different in each community; however, each community was given an iPad (Apple Inc) and Samsung S4 phone and an Aus $2000 (US $1419.60) budget to purchase resources for the Hub, such as books about dementia, web cameras, headsets, tablets, and items to assist people living with dementia (eg, simplified clocks, therapy dolls, and activities for people living with dementia). The Hubs were established, and volunteers received their training only when the community entered the intervention phase.

The Verily Connect app was developed and published on the web before the first intervention period wave. Selected screenshots of the Verily Connect app are provided in Multimedia Appendix 2. There were no substantial revisions or updates to the Verily Connect intervention during the trial. Carer participants were requested to use the Verily Connect app at least 4 times; however, they could decide how much or how little time they spent on each opening of the app. Carer participants were also asked to take part in at least one videoconferenced peer support group.

Comparators

During the control phase, informal carers and people living with dementia received their usual care and support, which differed in each community. Most communities did not offer specialist dementia support; they offered only general health care. However, two of the communities provided a specialist dementia support nurse on a part-time basis. In six of the communities, no carer support groups were operating. In 4 communities, general carer groups were available and, in 2 communities, dementia-specific carer support groups were offered. A usual practice comparator is considered the most appropriate approach for complex, nonpharmacologic interventions such as Verily Connect because other types of comparators are unfeasible [28]. When a community entered the intervention phase, they received usual care and support with the addition of the Verily Connect intervention strategies. For each of the 12 communities, the control phase was an 8-week preintervention wait period followed by the sequential stepped crossover to commence the Verily Connect intervention phase. All participating communities eventually received the Verily Connect intervention.

Study Setting and Participants

The study population comprised people in 12 rural communities in 3 Australian states (8/12, 67% in Victoria and 2/12, 17% in both New South Wales and South Australia). In each rural community, there were representatives from 3 subpopulations: service providers (*staff*), volunteers (*volunteers*), and informal carers of people living with dementia (*carers*). Having participants from 3 different stakeholder groups ensured that data on the effects of Verily Connect could be collected from each group's perspective.

Project Team

The project team included research officers, a project manager, a steering committee, and an advisory committee. A research officer was assigned to 2 or 3 clusters to coordinate project activities, promotion, participant recruitment, data collection, and regular engagement and contact with participants, including traveling to the communities as needed. A research project manager oversaw the operations of the research officers, presented at community meetings, facilitated videoconference meetings with groups of participants, and liaised with other stakeholders. A research steering committee met monthly to monitor the overall design and progress of the study. An

advisory committee met quarterly to provide input about the project from the perspective of app end users and participants; it comprised carers of people living with dementia and representatives from service organizations that supported people living with dementia and carers.

Randomization

The different participant groups had different roles during the Verily Connect intervention, which precluded randomization of individuals; however, it was possible to randomize the order in which the participating communities joined the intervention phase of the study. An independent consultant used stratified randomization to produce the schedule. Stratification was needed to ensure that only 1 community from the states of South Australia and New South Wales began in a wave as there was only 1 part-time research officer allocated for each of these states. It would have been impractical for 2 communities managed by the same research officer to commence the intervention within the same wave. The sequence in which communities would join the intervention phase was revealed to the project manager before the start of the trial so that the project manager could organize the logistics of implementing the intervention in the communities. The communities (including the participants) progressively learned the order of implementation immediately before the beginning of the next wave of intervention implementation. For example, at the beginning of wave 1, only the 3 communities that would commence the intervention in wave 1 were known. At the beginning of wave 2, the identities of the next 3 communities joining the intervention phase were revealed.

Inclusion Criteria

The Verily Connect intervention was designed to take action at the community level and, therefore, the parameters for inclusion were broad. Although it was anticipated that many carers would be aged >75 years as dementia disproportionately affects older people and it was anticipated that many carers would be spouses of people living with dementia, there were no specific age range requirements for carers other than being an adult (aged ≥18 years). In addition, the stage of dementia of the person living with dementia was not specified; all carers of people living with dementia were welcome to participate, including carers of people who were living with mild cognitive impairment. Although it is acknowledged that the needs of carers of people living with mild cognitive impairment and those living with dementia are different, both groups of people could elect to participate if they chose to as the study was a practical trial designed to intervene at the community level rather than solely targeting individuals. Allowing carers of people living with mild cognitive impairment was in keeping with the broad and inclusive intent of the project. The aim was to increase social support for carers no matter the stage of dementia of the person for whom they were providing care. The inclusion criteria for carers, volunteers, and staff are outlined in Textbox 2.

Textbox 2. Inclusion criteria for carers, volunteers, and staff.

Inclusion criteria for carers

- Self-identified carer for a person living with dementia or cognitive impairment
- Living in the community catchment area
- Willing to try the Verily Connect app on a smartphone or tablet with internet access or to use the website on a computer with internet access and willing to participate in peer support groups via videoconference on an electronic communication device with internet access and videoconferencing functionality

Inclusion criteria for volunteers

- Living in the community catchment area
- Willing to undertake training provided through the Verily Connect project
- Willing to assist people to learn to use web-based technologies

Inclusion criteria for staff

- Employed by a provider of a dementia service or service for older adults in the catchment area
- Access to a smartphone, tablet, or computer with internet access

Recruitment

Recruitment began 8 weeks before the start date for wave 1 of the implementation phase and continued until the end of wave 4. Recruitment was undertaken by conducting open community forums in each of the 12 participating communities. Additional recruitment strategies included meetings with community groups (eg, Lions Club, Probus, carers' support groups, and Country Women's Association), promotion via social media (Twitter and Facebook) and websites of partner health services, and press releases and advertising using news media (radio and print). Participant information and consent forms (Multimedia Appendix 3) were available at the recruitment meetings and provided to all potential participants. Potential participants were given the opportunity to discuss their participation with and ask questions to a research officer or the project manager; discussions were available face to face and by telephone. After the participants provided their written consent, the research officer assigned to the participant's community enrolled the participant.

Sample Size and Power

The sample size was based on an estimation of how many carers of people with dementia might be available to participate from a small rural community, the number of volunteers required to support the carers, and the number of health service staff who might have expertise in supporting people with dementia in a small rural community. At the time of the protocol development, there were no suitable studies to inform our sample size calculation. Therefore, a linear mixed effects model simulation (2000 replications), where the intervention and period effects were assumed to be fixed and the carer and community effects were assumed to be a random simulation, was used instead. The simulations were run in R (version 3.51; R Foundation for Statistical Computing). The assumptions were 12 rural communities with 12 carers from each community that contribute data at each of the 5 data collection periods, a difference in the mean MOS-SSS score of 9 [29] between the intervention and control phases, an SD of 24.2, an α of .05 for a 2-sided test, an intracommunity correlation coefficient of 0.01 and 0.05, and within-carer correlation (0.3, 0.5, and 0.7) for repeat outcome measures on carers (Table 1).

The study power was calculated as the proportion among all 2000 simulation runs of 2-sided *P* values for the estimated intervention effect that reached a nominal value of <.05. A total of 2000 replications were sufficient to estimate the power with a margin of error of 1.75% assuming the true power was 80% [30]. To allow for a dropout rate of 20%, recruitment targets were set per community at 15 carers, 3 health service staff, and 5 volunteers.

Table 1. Power calculations to detect an effect size of 9 (SD 24.2) between the intervention and control phases assuming an alpha of 5% for a 2-sided test for a stepped-wedge cluster randomized controlled trial with 12 clusters and 5 steps (including baseline).

Within-carer correlation	Within-community correlation	Sample cluster size[a]	Power[b]
0.3	0.01	12	0.80
0.5	0.01	12	0.89
0.7	0.01	12	0.98
0.3	0.05	12	0.78
0.5	0.05	12	0.88
0.7	0.05	12	0.97

[a]A total of 15 carers to be recruited at baseline to allow for 20% attrition over the study period.

[b]Power calculations based on 2000 simulations.

Outcome Measures

Primary Outcome

The primary outcome was the change in perceived carer social support as measured by the MOS-SSS [31]. The Zarit Burden Interview (ZBI) [32] was initially selected as the primary outcome, and the MOS-SSS was selected as a secondary outcome. However, 1 month into the trial, the MOS-SSS was elevated to the primary outcome and the ZBI became a secondary outcome as it had become clearer after further consultation with a biostatistician that carer support would likely be more amenable and responsive to the Verily Connect type of intervention than carer burden would.

Secondary Outcomes

The secondary outcomes are outlined in Textbox 3.

Textbox 3. Secondary outcomes of the study.

Secondary outcomes

- Additional quantitative measures collected by web-based survey:
  - Perception of carer burden, measured using the Zarit Burden Interview [32]
  - Self-reported use of services available in the community to support people living with dementia or cognitive impairment and their carers, measured using a purpose-designed questionnaire
  - Carers' use of information and communication technology, measured using a survey adapted from Predictors of older adults' technology use [33]
- Feedback about the experience of participating in Verily Connect activities from the perspective of carers and volunteers
- Process evaluation using the Consolidated Framework of Implementation Research [34]
- A cost analysis of the implementation of Verily Connect undertaken by a consultant health economist

Data Collection

Survey Data

Self-reported use of services in the community was developed as a purpose-designed survey as no other existing measure could be found that collected the specific data that were required. See Multimedia Appendix 4 and 5 for a copy of the survey questions.

A survey designed for older adults was used as the basis for questions about carers' use of ICT even though carers could be adults of any age. In the planning stages of the study, it was hypothesized that most of the carers who were likely to be involved in the study would be older people who were spouses of people living with dementia. The survey asks basic questions about ICT such as whether the carer has access to internet-enabled devices and what sort of device and whether the person had recently accessed the internet and, if so, what was the purpose of using the internet (see Multimedia Appendices 4 and 5 for a copy of the survey questions). This survey was written with older people in mind; however, it does not preclude younger people, and the survey assessed access to and use of ICT in a way that did not require technical knowledge or previous experience with using ICT.

Data were collected from carer participants through web-based surveys completed at 6 times. The first 5 were within the trial period, and the final time was 6 months after the end of the trial. The researchers emailed the participants the link to complete the appropriate survey on the web, as shown in Table 2.

Survey 1 can be found in Multimedia Appendix 4. Surveys 3, 5, and 6 were the same and can be found in Multimedia Appendix 5. Surveys 2 and 3 consisted only of the MOS-SSS. The demographic information that was collected only during survey 1 was age, gender, identification as Aboriginal or Torres Strait Islander, languages other than English spoken at home, postcode, highest level of educational attainment, relationship of the carer to the person living with dementia, length of time in the caring role, and an open-ended question about what the participant considered a dementia-friendly community to be. Background information that was collected during survey 1 and surveys 3, 5, and 6 was information about whether the carer or person living with dementia had a Health Care Card, Private Health Insurance, or a Home Care Package; whether the person living with dementia had received a diagnosis of dementia; where the person living with dementia resided in relation to the carer; whether emergency care had been used in the previous 2 months; what health and community services had been used in the previous 2 months and who had organized access to these services; whether other services were needed or received; whether access to services was easy or difficult; and the rating of the dementia-friendliness of the participant's local community.

Table 2. Web-based carer survey collection periods and content.

	Collection period	Survey content
Survey 1	August 20 to August 31, 2018, or when the participant first joined	• MOS-SSS[a] • ZBI[b] • Initial demographic and background information • Perception of social connection
Survey 2	October 15 to October 26, 2018	• MOS-SSS
Survey 3	December 10 to December 21, 2018	• MOS-SSS • ZBI • Ongoing background information • Perception of social connection
Survey 4	February 4 to February 15, 2019	• MOS-SSS
Survey 5	April 1 to April 12, 2019	• MOS-SSS • ZBI • Ongoing background information • Perception of social connection
Survey 6	October 7 to October 18, 2019	• MOS-SSS • ZBI • Ongoing background information • Perception of social connection

[a]MOS-SSS: Medical Outcomes Study-Social Support Survey.

[b]ZBI: Zarit Burden Interview.

Feedback Data

Informal feedback from all types of participants was collected and recorded as memos by the research team throughout the study period. Memos were written about ad hoc feedback on the Verily Connect app (eg, if a service was missing or a link did not work). Memos were also written after routine follow-up by the research team (eg, feedback about whether a participant had been using the Verily Connect app, if they had experienced

any problems using the app or connecting to videoconference meetings, or if they had had a good experience using the app).

Formal feedback was collected via focus groups with volunteers at the end of the implementation period (April 1-12, 2019). The focus groups were conducted by videoconference. Volunteers were asked about their experience of volunteering for Verily Connect (see Multimedia Appendix 6 for the focus group questions). During the follow-up period (September 2019-October 2019), formal feedback was collected by individually interviewing all participants (see Multimedia Appendix 7 for the interview guide). The carer, volunteer, and staff participants were asked about their use of the Verily Connect app after the end of the implementation period and whether they had any additional feedback on or suggestions to improve Verily Connect.

Feedback was included as a secondary outcome measure as it provides a description of the participants' perceptions and perspective of the Verily Connect intervention. As the Verily Connect intervention was an innovation in carer support, the collection of detailed feedback enabled a more comprehensive and nuanced understanding of the effects of the intervention to be gathered.

Process Data

The Consolidated Framework of Implementation Research (CFIR) is a framework of ideas for preparing for and evaluating the implementation of innovations [35]. The CFIR Interview Guide Tool [36] was used to create an interview guide (Multimedia Appendix 8) to examine the implementation of Verily Connect. Interviews with staff were completed at the end of the implementation period (April 1-12, 2019). The interviews were conducted via videoconference or telephone.

Economic Data

Data for the cost analysis were collected by Verily Connect project staff about the time they spent completing Verily Connect implementation activities and the resources needed to support this work (eg, office space, travel costs, and room hire).

Data Analyses

Analysis of Survey Data

The demographic data, participant reports of using technology, and perceptions of social connection were descriptively analyzed. A method suggested by Hussey and Hughes [37] using a basic model-based approach for analyzing data from a cross-sectional stepped-wedge cluster randomized controlled trial was initially planned. However, owing to difficulties with recruitment, there were insufficient samples for this method to be viable; only those participants who completed the MOS-SSS and ZBI on occasions before and after receiving the Verily Connect intervention were included. Missing data were managed by first using the guidelines for handling item- and construct-level missing data as described in the manuals for scoring the assessment instruments. Next, where participants completely failed to provide data (person-level missing data), a pairwise deletion approach was adopted. The difference between pre- and postintervention results for the MOS-SSS and ZBI was tested for statistical significance using a 2-tailed paired *t* test.

Analysis of Qualitative Feedback

All qualitative data were collected as text (memos were already in written form, and interviews and focus groups were transcribed verbatim). The texts were imported into NVivo (QSR International); a separate NVivo project was created for each category of participant: one for carers, one for volunteers, and one for staff. Data were initially sorted into codes as described by Miles and Huberman [38] and Stanley [39]. The coding framework was derived based on questions asked of participants, such as what type of device the participants used, how often they used the Verily Connect app and for what purposes, what they thought worked well about the Verily Connect model and what did not work well, and whether they had any suggestions for improving the Verily Connect app or model. Inductive analysis and coding were also completed. Codes were inductively developed from issues that were raised by participants; for example, the participants' experiences of caring, their preferences for receiving support, and their experiences and perceptions of using technology to receive support.

The qualitative analysis was led by an experienced qualitative researcher (CW), who established the coding framework. Research officers assisted with reviewing the data and coding. CW completed further iterative data reduction, categorization, and theming using qualitative analysis techniques described by Streubert and Carpenter [40], Silverman [41], and Braun and Clarke [42,43]. Data saturation was not used as a stopping point for data analysis; all available data were analyzed. The findings were discussed by the research team, and all team members were involved in the final reporting.

Analysis of Process Data

The verbatim transcripts of staff interviews were qualitatively analyzed using the CFIR framework [44]. A CFIR codebook, descriptions, and NVivo template were downloaded from the CFIR website [44]. CW led the analysis process. Research officers assisted with the coding process using the CFIR codebook, descriptions, and template. Further iterative analysis, categorization, theming, data reduction, and selection of data for reporting were completed by a small team of researchers (CW, DM, and IB). All available data were analyzed. The final findings were discussed by the research team, and all team members were involved in the final reporting.

Analysis of Economic Data

A health economist created a data collection template to collect and collate resource use information according to input cost classifications. The development of the template drew heavily on the cost classification scheme outlined by the World Health Organization [45]. Research officers populated a template for each of the 12 communities. Overhead cost data that were relevant to the entire study and all 12 communities were also collected: (1) website and mobile app development, (2) advertising and promotion, (3) training development, and (4) communications. The health economist used these data to

estimate the resources that would be required to implement Verily Connect in a nonresearch environment.

Results

Data collection commenced in August 2018 and concluded in September 2019. The total number of participants was 113, comprising 37 (32.7%) carers, 39 (34.5%) volunteers, and 37 (32.7%) staff members. Target numbers for volunteer and staff participants were achieved; however, the number of carer participants was lower than was hoped for. The study was complicated to implement because of the lengthy time frame, the variety of participants (carers, volunteers, and staff) who had different roles to play, the heterogeneous nature of the participating rural communities, and the fact that the research team was geographically dispersed. Differences in government, health, and community organizations and modes of operating across the 3 states of Australia added to the complexity of implementing the study. Even within states, each of the 12 communities was distinct and differed from other communities according to geography, population size and profile, and health and community support available. The research team comprised researchers from 5 universities across 3 time zones and separated by hundreds of kilometers.

Variability across the communities was managed by allowing each community some flexibility regarding the implementation of the Verily model in the local community. For example, in Victor Harbor, two of the volunteers were a couple and worked together to assist people in their community to use Verily Connect. In addition, Victor Harbor was well-supported by active face-to-face carer support groups, so some of the carers in that community elected to continue attending their local carer support groups rather than the web-based support provided by Verily Connect. In Kooweerup, the health service leveraged interest in the Verily Connect project to springboard the development of a local dementia-friendly café that offered face-to-face social support for people living with dementia and carers.

Web-based technology in the form of the Verily Connect app was used as the main method of adding to the support received by the carer participants. Other web-based ICT was used to facilitate communication between the participants and the research team and between research team members.

A study report provided to the funding body is available on the web [46]. More detailed publication of the results is anticipated to be completed by June 2022.

Discussion

Principal Findings

This study aimed to develop and implement the use of web-based interventions to add to the support provided to informal carers of people living with dementia in rural communities and evaluate the developed Verily Connect program by measuring changes to carers' perceived support as measured by the MOS-SSS. The purpose of this manuscript was to detail the methods that were used to undertake this study and, therefore, the results of the evaluation of the Verily Connect program have not been presented here but are anticipated to be discussed in future publications. As illustrated in the presentation of the study methods, the study design was quite complicated—there were 3 types of participants, and each participant group had a different role to play in the study; 12 rural communities participated in the study and were geographically dispersed across 3 states of Australia; the study took place in a community setting rather than in a laboratory or health care service; and effort was made to include carers of people living with dementia in the design of the Verily Connect app, its implementation, and the research process.

The study was complex and, therefore, challenging to implement. Although a less complex study would have been easier to complete, the complexity of the study was representative of the complexity of the phenomenon being studied. Support for informal carers of people living with dementia in rural areas of Australia is heterogeneous and messy and involves multiple stakeholders. Just as the phenomenon is complex, solutions for increasing support for informal carers are also complex and, therefore, using a simpler type of research design would have run the risk of oversimplifying the phenomenon and may have resulted in poorer-quality data.

The Verily Connect model leveraged web-based ICTs to overcome challenges to service delivery in small rural communities, especially reducing the need to travel to access dementia-specific services and gathering information about local and national services in one place. Web-based technologies were also used to facilitate research teams across multiple universities and separated by geography to collaborate and work effectively together. Further web-based technologies were used to facilitate the support of and efficient sharing of information between volunteers and health services across 3 states of Australia. The use of these technologies provided a solution for assisting geographically dispersed groups of people to collaborate, share ideas, and support each other and, thus, they are equally important in the time of physical separation created by the need to reduce social contact to avoid spreading a socially transmitted virus such as COVID-19.

The use of a stepped-wedge cluster design enabled the evaluation of the Verily Connect app in a real-world setting. The rural communities that participated as clusters in the trial were diverse in terms of geographical and population profile, access to services, funding, and infrastructure. Thus, when developing and trialing the Verily Connect implementation, there was a need for the model and the evaluation to be flexible and dynamic to meet the needs of the different local populations. Thus, flexibility was built into the Verily Connect implementation model so that each community had a license to tailor the implementation to their community.

The research was undertaken using a co-design and coproduction philosophy [47,48]. Open public forums were held at the beginning of the project to gather perspectives, needs, and ideas from carers, service providers, and community members. Throughout the project, coproduction approaches were used, such as the ongoing adaptation of the Verily Connect model based on feedback collected and challenges encountered. There was engagement with key stakeholders, including rural

community members and local organizations, Dementia Australia, Carers Australia, the Commonwealth, state and local governments, and rural service providers. At the conclusion of the project, preliminary findings were shared with each community.

The aim of testing the Verily Connect model in a variety of rural communities was to learn how the model could be adapted to a wide range of rural communities, anticipating that the model might be scaled up to national implementation. To this end, a toolkit was developed to enable communities to join the web-based dementia-friendly Verily Connect community and establish a local geographical dementia-friendly community [49].

Limitations and Strengths

A limitation of the project was the small number of carer participants in each cluster. Recruitment of carer participants was very challenging. Potential participants were dissuaded from taking part because of feeling overwhelmed with caring responsibilities and lack of interest or confidence in using web-based technology. The time and effort needed for recruitment and onboarding of participants was initially costly as the research team needed to travel long distances to meet face to face with the communities. Costs could be reduced in future iterations of the project if recruitment and onboarding activities are moved to the web-based environment.

As the intervention extended over a long period (32 weeks), not all participants were able to commit to taking part for the full length of time. Life events such as illness and changed personal, work, and social circumstances sometimes meant that participants needed to exit the study earlier than anticipated, resulting in less comprehensive data collection than was desired and planned for.

A strength and limitation of this project was the engagement of the *whole of rural community*; that is, multiple community stakeholders and community groups were involved. This was a strength as it meant that a variety of different users' perspectives was evaluated and, practically, the implementation of the intervention did not have to be too tightly controlled. In a small rural community where the number of carers of people living with dementia is low, having an inclusive approach to recruitment increased the likelihood of recruiting a larger sample size. However, this approach was also limiting as it meant that information about caring and care support was broad. Thus, the care needs of individual carers may not have been met.

A limitation of the study was that randomization of communities was limited by the practical challenges of implementing the study. Owing to the nature of the intervention, the participants were not blinded to whether their community was in the control or intervention phase.

Conclusions

This protocol provides an example of a study designed for real-world testing and the development of novel strategies intended to increase the support and information provided to informal carers of people living with dementia in small rural communities in Australia. This was a large and complex study addressing a health and care issue that will be of increasing significance to ageing societies such as Australia. This protocol illustrates some of the challenges and some examples of potential solutions for researchers who are engaging in complicated studies of intricate real-world situations.

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Authors' Contributions

All authors contributed to the conceptualization of this study and the writing of the protocol, either directly or by reviewing the manuscript.

Conflicts of Interest

The authors created the Verily Connect app and its implementation program.

Multimedia Appendix 1
Diagram of stepped-wedge control and implementation periods.
[PNG File , 53 KB - resprot_v11i5e33023_app1.png]

Multimedia Appendix 2
Screenshots of the Verily Connect app.
[PDF File (Adobe PDF File), 1250 KB - resprot_v11i5e33023_app2.pdf]

Multimedia Appendix 3
Participant information and consent form for carers.
[PDF File (Adobe PDF File), 159 KB - resprot_v11i5e33023_app3.pdf]

Multimedia Appendix 4
Survey completed when carer participants first joined the study.
[PDF File (Adobe PDF File), 843 KB - resprot_v11i5e33023_app4.pdf]

Multimedia Appendix 5
Survey completed by carer participants at data collection timepoints 3, 5, and 6.
[PDF File (Adobe PDF File), 798 KB - resprot_v11i5e33023_app5.pdf]

Multimedia Appendix 6
Focus group question guide for volunteer participants.
[DOCX File , 14 KB - resprot_v11i5e33023_app6.docx]

Multimedia Appendix 7
Interview question guide for feedback from all participants at follow-up.
[DOCX File , 16 KB - resprot_v11i5e33023_app7.docx]

Multimedia Appendix 8
Interview question guide for staff participants based on the Consolidated Framework of Implementation Research.
[DOCX File , 18 KB - resprot_v11i5e33023_app8.docx]

Multimedia Appendix 9
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1233 KB - resprot_v11i5e33023_app9.pdf]

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Abbreviations

CFIR: Consolidated Framework of Implementation Research
ICT: information and communication technology
MOS-SSS: Medical Outcomes Study-Social Support Survey
ZBI: Zarit Burden Interview

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Protocol

Long COVID Optimal Health Program (LC-OHP) to Enhance Psychological and Physical Health: Protocol for a Feasibility Randomized Controlled Trial

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Abstract

Background: Long COVID is a collection of symptoms that develop during or following a confirmed or suspected case of COVID-19, which continue for more than 12 weeks. Despite the negative impact of long COVID on people's lives and functioning, there is no validated treatment or even rehabilitation guidance. What has been recommended thus far is the adoption of holistic management approaches. The Optimal Health Program (OHP) is a brief 5-session, plus booster, psychosocial program designed to support mental and physical well-being that has been used effectively for a range of chronic conditions.

Objective: This study examines the feasibility and acceptability of employing an especially customized version of OHP (long COVID OHP [LC-OHP]) to improve psychological and physical health of people with long COVID.

Methods: This is a feasibility randomized controlled trial that will be running from November 2021 to February 2023. Eligible participants aged 18 years or older who are experiencing symptoms of long COVID will be identified through their secondary practitioners with recruitment to be undertaken by the research team. A total of 60 participants will be randomized into a control (usual care) or an intervention (LC-OHP) group. Outcomes will be feasibility and acceptability of the program (primary); and efficacy of the LC-OHP in improving anxiety, depression, fatigue, self-efficacy, and quality of life (secondary). Up to 20 participants will be interviewed at the end of the trial to explore their experience with the program. Quantitative data will be analyzed using SPSS, and differences between groups will be compared using inferential tests where appropriate. Qualitative data will be transcribed and thematically analyzed to identify common emerging themes.

Results: This is an ongoing study, which began in November 2021.

Conclusions: Long COVID has a significant impact on an individual's mental and physical functioning. The LC-OHP has a potential to provide people living with long COVID with additional support and to improve self-efficacy. The findings of this study would identify the feasibility of delivering this program to this population and will provide an indication for the program's effectiveness.

Trial Registration: ISRCTN Registry ISRCTN38746119; https://www.isrctn.com/ISRCTN38746119

International Registered Report Identifier (IRRID): DERR1-10.2196/36673

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KEYWORDS

long COVID; COVID-19; optimal health program; telemedicine; integrated care; telehealth; patient care; health intervention; mental health; physical health; psychological health; pandemic; patient support

Introduction

Background

COVID-19, as named by the World Health Organization, is a novel virus that emerged in Wuhan, China in December 2019 and spread rapidly across the whole world resulting in a global pandemic [1-3]. From the start of the pandemic to date, there are more than 246 million confirmed cases of COVID-19 across the world, of which there is around a 90% recovery rate, although more than 4 million people have died [4,5]. Several measures have been implemented to limit its spread, including avoidance of public contact, maintaining social distance, case detection, contact tracing, the use of personal protective equipment such as face masks, and encouraging hand hygiene practices [6,7].

COVID-19 infection is generally believed to be a short-term illness, from which people recover in about 2 weeks [8]. Figures indicate that around 80% of affected people develop a mild to moderate disease, and 5% of those with severe disease develop a critical illness [9]. Recovery usually takes 7-10 days following the onset of the mild infection and 3-6 weeks in the severe or critical illness [10]. In some people, certain symptoms persist in the postacute phase [11,12]. This condition has been given several labels, including long COVID, post-COVID syndrome, long haulers, postacute COVID-19, and persistent COVID-19 symptoms [11,13,14]. Whatever the term, each describes an illness in which symptoms persist longer than expected, or where there are lasting effects of the infection [2]. In the absence of an alternative explanation, long COVID encompasses ongoing symptoms of COVID-19 lasting 12 weeks or more [2,12,15-18].

COVID-19 is a new virus; as such, there are many unknown aspects surrounding its trajectory, including who is susceptible to long COVID and why recovery is prolonged for some people. While it is not yet possible to identify who may develop long COVID, there appears to be several risk factors including female sex, increased age [15], presence of more than 5 symptoms in the acute phase [19], associated comorbidities, and extended duration of acute illness [14,19-23].

A recent systematic review, which included 25 studies with 5440 participants, reported the frequency of long COVID to be up to 80% of the included population [17]. Another study showed that some symptoms persisted 3 months post hospital discharge [24]. Moreover, it seems that anyone can develop long COVID, including young people with no preexisting health conditions [18,25]. In the United Kingdom, the Office of the National Statistics and the UK COVID-19 symptom study app show that 1 in 5 people have COVID-19 symptoms that persist after 5 weeks, and 1 in 10 have symptoms that persist longer than 12 weeks [8,26]. To date, more than 8 million cases of COVID-19 have been confirmed in the United Kingdom [5], with more than 2 million people reporting they may have had long COVID [27], but the number is expected to increase as the virus is still active in the community.

Symptoms of long COVID vary between individuals. It seems to affect multiple organ systems in the body, and patients can present with single, multiple, constant, transient, or fluctuating symptoms [12,28], in a continuous or a relapsing and remitting course. According to a recent meta-analysis, the five most commonly reported symptoms are fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%), and dyspnea (24%) [13]. Fatigue was found to be independent of the severity of the initial viral infection and to develop irrespective of a preceding hospitalization [29]. Long COVID represents a challenge for both the patient and the health care provider as it can be difficult to diagnose with certainty and may influence the doctor-patient relationship and trust [30]. Other reported manifestations of long COVID include cough, joint pain, chest pain, and low-grade fever [8,31,32].

Encountered neuropsychiatric symptoms include anosmia, brain fog, and neuropathy [33,34]. COVID-19 doubles the risk of developing a psychiatric disorder [35]. Anxiety, depression, or posttraumatic stress was manifest in 56% of patients with long COVID [36]. Social isolation, decreased physical activity, changed habits, as well as social and economic insecurity that are associated with the pandemic may contribute to developing the physical and psychological symptoms of long COVID [17,37].

The lack of sufficient information on this condition, along with variability in presenting symptoms and disease course between individuals, adds further challenges to identifying the best practice for its management and control. To date, no clear treatment regime is available to mitigate long COVID, and treatments given are dependent on presenting complaints. Minor complaints such as fever or cough can be treated symptomatically with paracetamol, cough suppressants, or antibiotics if a secondary bacterial infection is suspected [14]. Patients are advised to follow the “three P’s principle,” which is as follows: “Pace” to conserve energy when doing daily activities; “Plan” activities across the week; and “Prioritize” necessary tasks to get a mixture of activities that will boost mental health every day [38].

The complexity and diversity of symptoms of long COVID demand the use of individualized care plans [39]. The focus should not be on providing symptom by symptom management, but rather on delivering holistic, integrated care, bringing together patients and health care practitioners from across all specialties to achieve a common goal and meet the long-term needs of this population [11,40,41]. In the United Kingdom, a 5-point plan was recently set by the National Health Service (NHS) in response to the challenge of long COVID [18]. This included the launch of several clinics to tackle the persistent symptoms of COVID-19 [18,31], the creation of “Your COVID Recovery” website that provides reliable and up-to-date information and support [42], and the investment of millions of pounds in research to gain better understanding of this condition. Additionally, guidance was published to support

clinicians in providing care to patients with long COVID [12,43].

Attention to mental health is also important as restrictions associated with the pandemic limited the provision of mental health services [44-46]. Although at the beginning, accessing mental health services decreased [47], numbers slowly started to increase and are now at a record high [47-49]. In 2020, the Office of the National Statistics reported that well-being levels were at their lowest since data collection started in 2011 [50], and that this has been greatly influenced by the pandemic. There has been a significantly increased demand on local beds [51], and the need for new or additional mental health support is expected to increase over the next 3 to 5 years [52,53] to a level that is 2 to 3 times that of the current NHS capacity [54]. There is an obvious and critical need to provide alternative supports; integrated, psychological, and mental health support that is readily accessible to all patients.

Long COVID highlights the need for a specialized intervention to manage complex comorbidities. In this context, the Optimal Health Program (OHP) is a form of psychosocial intervention [55] that provides clinicians with a consistent approach to support patient self-management. This approach challenges traditional methods of health care by encouraging patients to be actively involved in their own management [56] as this is anticipated to be more effective than using passive approaches [57]. The OHP has been shown to be beneficial for people with other chronic conditions such as diabetes [58], stroke [59], and chronic kidney disease [60]. However, no research has yet evaluated its use in patients with long COVID. The Long COVID OHP (LC-OHP) program aligns with the NHS and the National Institute for Health and Care Excellence (NICE) guidelines for managing and supporting long COVID by promoting shared decision-making and by delivering care that meets the individual needs and preferences of patients. Additionally, it provides care to patients in an easy-to-understand way and signposts them to useful resources for more support, as recommended by current guidelines [61].

Through the application of the tailored LC-OHP sessions alongside those living with long COVID, this study will examine if this program is feasible and acceptable in improving individual's psychological and physical health.

Aim and Objectives

This study aims to examine the feasibility and acceptability of the LC-OHP and evaluate any impact on quality of life, depression and anxiety, fatigue, and self-efficacy in patients with long COVID, compared to usual care. The study objectives are as follows:

Primary Objectives

The primary objectives are to determine the feasibility of conducting a 5-week psychosocial intervention in patients with long COVID by identifying the following outcome measures: (1) acceptability, recruitment, and retention rates; (2) participant's satisfaction with the intervention; and (3) appropriateness of secondary outcome measures.

Secondary Objectives

The secondary objectives are to evaluate the preliminary efficacy of the LC-OHP in improving quality of life, depression and anxiety, fatigue, and self-efficacy in people with long COVID, compared to usual care.

Methods

This protocol is reported using the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) reporting guidelines [62].

Research Design and Setting

This research is a feasibility randomized controlled trial to be conducted from November 2021 to February 2023 by investigators from the University of Suffolk. Potential participants will be identified from a long COVID clinic located within a hospital setting.

Participants

Inclusion Criteria

Patients meeting the following criteria will be included in the study: (1) adults ≥18 years old; (2) COVID-19 infection confirmed through polymerase chain reaction testing or clinical diagnosis from a general practitioner; (3) experiencing post–COVID-19 syndrome (as defined by NICE 2020) 12 weeks or more following onset of symptoms or confirmed through testing; (4) able to participate in a telephone interview in English language (or with accommodated adjustments); and (5) able to consent to participate in the study.

Exclusion Criteria

Patients will be excluded if they meet any of the following criteria: (1) children and young adults (17 years and under); (2) unable to consent to participate in study; and (3) unable to participate in a telephone interview in English language.

Sample Size

A total of 60 patients will be recruited to the trial, with 30 randomized to the intervention or control group. The sample size has been determined according to the recommendations that at least 30-35 patients be included per group for pilot and feasibility studies [63-66].

Study Procedures

Consent and Recruitment

Eligible participants who are referred to the long COVID clinic will be identified and approached by the clinical team on their initial visit to the clinic that is located at a hospital setting. As part of their initial assessment, the team will provide a brochure that outlines the trial and details of the research team to contact if they would like to take part. After expressing interest, the research team will provide eligible participants with the trial's participant information leaflet and a consent form with a prepaid envelope. The research team will then contact the participants after 5 working days of sending the documents to answer any queries and to remind them to send their signed consent form.

Baseline Data Collection

Following the receipt of signed consent forms, the research team will contact participants to agree on the logistics of completing the questionnaires. Questionnaires will be sent to participants by email or post. With the baseline questionnaire, participants will also complete a short questionnaire to collect demographic data (ie, age, gender, ethnicity, and education). Participants will also have the option to complete the questionnaires on their own (ie, self-completion) or by telephone supported by a member of the research team. Responses to questionnaires will be recorded on a secure electronic database. Two reminders will be sent to nonrespondents. If no response is received, participants will be removed from the study. Table 1 provides a summary of the questionnaires to be completed by participants in the study at baseline, 3 months, and 6 months post randomization.

Table 1. Overview of questionnaires.

Questionnaire	Outcome	Details
PHQ-9[a]	Depression	A 9-item validated questionnaire with 4 response options: “not at all” (scored as 0) to “nearly every day” (scored as 3). PHQ-9 total scores range from 0 to 27, with scores of ≥5, ≥10, and ≥15, representing mild, moderate, and severe levels of depression severity [67]. The questionnaire can be administered over the phone.
GAD-7[b]	Anxiety	A 7-item, easy-to-use, self-administered questionnaire, answered using a 4-point scale (from 0 to 3). It is used as a screening tool and severity measure for generalized anxiety disorder [68,69].
GSE[c]	Self-efficacy	A 10-item questionnaire rated using a 4-point Likert scale (“not at all true” to “exactly true”). The questionnaire tests the individual’s self-efficacy (ie, his or her ability to organize and execute certain behaviors that are necessary in order to produce given attainments). Higher scores are indicative of higher self-efficacy. The questionnaire is valid and reliable with high internal consistency [70].
EQ-5D-5L[d]	Quality of life	A validated 5-item questionnaire scored on 5-item answers. It provides a generic measure on the following health dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression [71]. The questionnaire also includes a visual analogue scale with scores ranging from 0 to 100 to reflect current health status [72].
FAS[e]	Fatigue	A validated 10-item questionnaire that is answered using a 5-point answer scale: “never” (scored as 1) to “always” (scored as 5) [73,74].

[a]PHQ: Patient Health Questionnaire.

[b]GAD-7: Generalized Anxiety Disorder.

[c]GSE: General Self-Efficacy.

[d]EQ-5D-5L: European Quality of Life 5 dimensions, 5 levels.

[e]FAS: Fatigue Assessment Scale.

Randomization, Allocation, and Blinding

Participants will be randomized following the receipt of baseline data to either intervention or control group using a computer-generated block randomization. To avoid bias, an independent person will carry out participant randomization. Due to the nature and length of the intervention, it is not possible to blind either the research team or the participant to the treatment allocation.

Participants allocated to the control group will receive usual care provided to patients with long COVID, depending on presenting complaints and assessments. The intervention group will receive the LC-OHP plus usual care.

Intervention

The OHP is a person-centered model that focuses on health as defined by patients. It aims to support people with mental or physical illness by using a collaborative therapy–based self-efficacy intervention [55,75-78]. The program addresses psychological and physical dimensions of health [60], is flexible, and can be delivered by a range of practitioners. It can also be delivered at all stages of the care trajectory; in inpatient and outpatient settings, at homes, or by video conferencing, and to groups or to individual patients [77]. By enhancing self-efficacy and self-management skills, the program works on shifting the focus of an individual’s illness from being “dependent on services” to being “supported by services” [78], which is thus anticipated to reduce pressure and financial demands on health care systems.

The OHP can be delivered in 8- or 5-session sequential formats, with both types of delivery including a follow-up “booster session” [55] [77-80]. It offers its users (ie, facilitators and participants) a written booklet that includes different skills and information to support self-efficacy, besides regular reviews of previous sessions to follow progress [55]. In this trial, recognizing that fatigue is a core component, the LC-OHP will be delivered in 5 sequential sessions. The program’s key elements are summarized in Table 2.

Table 2. LC-OHP[a] sessions.

Session	Title	Content
1	Optimal health	• What is optimal health? • Optimal health wheel
2	I-Can-Do-Model	• Strengths and vulnerabilities • Stressors and strategies • Health plans 1 and 2
3	Factors of well-being	• Medication and metabolic monitoring • Collaborative partners and strategies • Health Plan 3
4	Visioning and goal setting	• Defining change • Orientation and preparation • Creative problem-solving and goal setting • Reflection and celebration
5	Building health plans	• Health plans 1, 2, and 3 • My health journal
Booster	Reflecting on the learning in the transformational journey to sustain well being	• Reflecting on learning in the transformational journey to sustain well-being

[a]LC-OHP: Long COVID Optimal Health Program.

Sessions will be delivered weekly with a booster session to be held 3 months after the last session. The booster session will target reviewing health plans and reflecting on achievements made toward health-related goals. Sessions will be held either in a 1:1 encounter with the facilitator, or in groups, or using a mixture of both, depending on participants' preferences. Each 1:1 session will last up to one hour, with breaks provided upon participant's request, and if necessary, the session can be completed at another time. Group sessions will last up to 90 min, and breaks will be provided upon request. Sessions will be held online (using a convenient platform) or by telephone (to those who do not have access to online facilities). Sessions will be audio-recorded to be checked by another member of the research team to confirm fidelity of program delivery. Participants can contact facilitators between the sessions if they have any questions or wish to change the time for the next session.

Facilitators have received prior training in delivering the program during a 2-day workshop delivered by one of the investigators (DJC) who developed the OHP program. Regular supervision will also be provided to facilitators to ensure fidelity with program delivery and to discuss any concerns. Additionally, a fidelity checklist will be completed by the facilitator after the end of each session to ensure all core components of each session have been covered. The checklist will also be reviewed by another member of the research team to ensure fidelity.

Quantitative Data Collection

Following participation and baseline data collection, the research team will contact participants at 3-month intervals after randomization at a prearranged time to complete the questionnaires detailed in Table 1. At the end of the trial, participants in the intervention group will be asked to evaluate the LC-OHP by completing the Course Experience Questionnaire.

Qualitative Interviews

After the end of the trial, participants allocated to the intervention group will be invited to participate in a semistructured telephone interview conducted by an independent researcher (not the OHP facilitator). The interview will target exploring participants' experience with the LC-OHP, identify their views on the program, and share any suggestions for improving the program for the future. Interviews will be audio-recorded and will be conducted at a time convenient to the participant. Interview duration will last up to 30 min (a max of 40 min if a participant requests more time) and will be guided by a topic guide developed by the research team. Participants will be interviewed until data saturation is reached. Textbox 1 shows a summary of the interview topic guide list.

Textbox 1. Summary of the interview topic guide list.

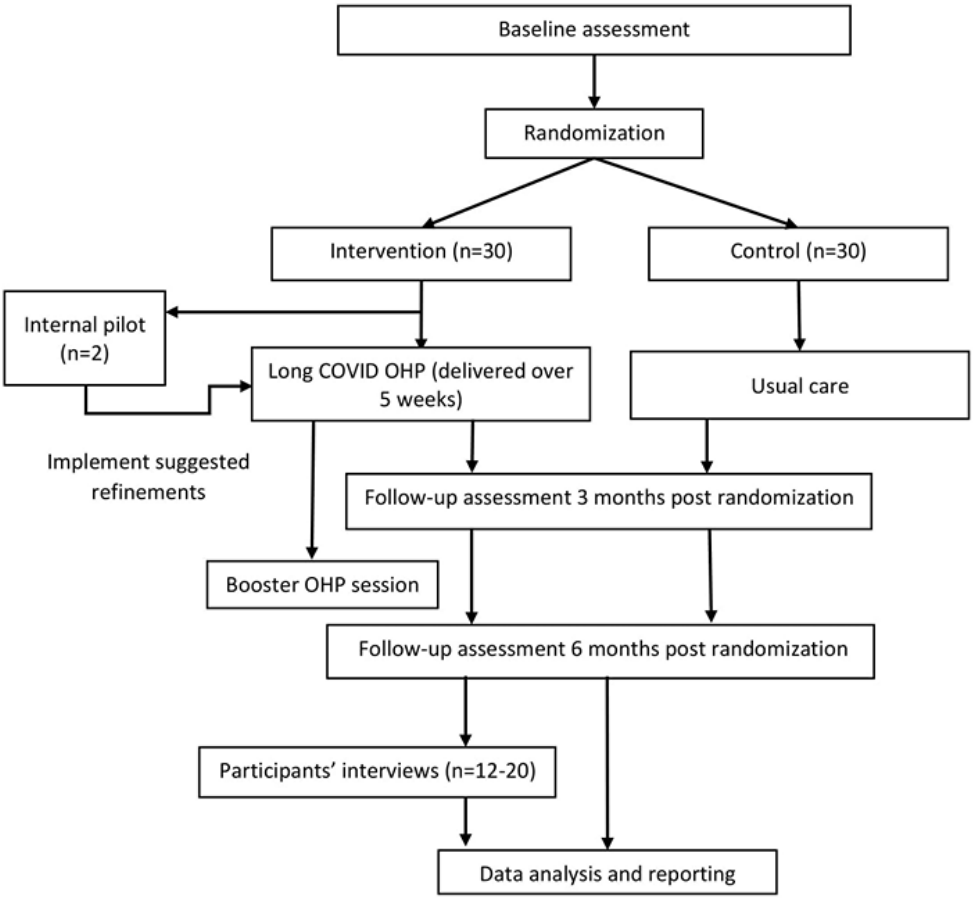
Main questions

- Can you please tell me a little bit about why you agreed to take part in the study?
- Describe your experience of being involved in the program.
- What do you think about the materials and support provided throughout the program?
- Do you feel that there may be changes that could be made to the program? What, how, and why?

Internal Pilot

The trial will start with an internal pilot, with the first 2 participants receiving a 1:1 session delivery. These participants will have a short interview (10 min) at the beginning of each session by the facilitator to identify their views about the previous session with respect to the program's materials and to inform any necessary refinements before starting the program with other participants. The program will start 2 weeks following the internal pilot in order to give enough time for any modifications to be implemented. Figure 1 presents a flowchart of the trial process.

Figure 1. Participants' flow in the study. OHP: Optimal Health Program.



Participant Withdrawal

Participants can leave the study at any time without their care being compromised. All data collected from participants prior to withdrawal will be included in the analysis.

Participants' withdrawals will be noted, and reasons will be classified under the following categories: (1) illness or death; (2) dropout or relocation; (3) loss of contact; and (4) failure to return the questionnaire.

Additionally, for the purpose of ensuring fidelity, the trial's research team will interview a sample of participants who withdrew from the intervention to identify reasons behind their withdrawal, and to collect any suggestions that may improve the program for future participants. The withdrawing participants will be free to decline this interview without their usual care being affected.

Data Analysis

Quantitative data analysis will be performed using SPSS (IBM Corp). Descriptive data will be presented using means, interquartile range, and percentages. Differences between the groups will be compared using appropriate inferential tests.

For the qualitative data, interviews will be recorded (with informed consent), transcribed verbatim, coded, and thematically analyzed (using an inductive thematic analysis approach) to identify common emerging themes [81]. Transcripts will be continuously revisited, and the accuracy will be verified by listening to the recordings and comparing them with the transcripts. Coding of data will be conducted using NVivo (QSR International), and codes will be checked by another member of the research team to ensure appropriate and consistent coding process. Any disagreements will be resolved by consensus, and by referring to the transcripts and original recordings.

Data Management and Monitoring

All data collected from participants will remain strictly confidential, and all participants will be pseudonymized and coded with a study number. Data will be securely stored at a central computer drive accessible only to members of the research team. Principles of the General Data Protection Regulation 2018 will be followed with respect to data storage, processing, and destruction. Any paper documents will be stored

in a securely locked filing cabinet located at the Integrated Care Academy at the University of Suffolk, accessible only to members of the research team.

A Data Management Committee (DMC) is set for the trial and will include the sponsor, 2 clinicians, 2 independent researchers, and 2 members of the public. The committee will meet at least 3 times (at the start, middle, and end of the trial) and as needed. The DMC will oversee all aspects of the study and will monitor the trial's progress and deadlines adherence, ensuring participant safety is maintained and agreeing on any amendments to the protocol. Any amendments conducted will be notified to ethical committees.

The trial will be prematurely terminated if severe and unacceptable safety risks occur. Adverse events will include any unfavorable and unintended events experienced by a participant during the study that are reported by the participant or observed by the investigator or medical staff. Serious adverse events will be any untoward medical occurrence that could result in death, hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, or a congenital anomaly or birth defect. Adverse events and serious adverse events will be registered and presented to the DMC to be reviewed. The DMC will have the power to stop the trial on safety grounds. However, it is highly unlikely for early termination as the OHP has been previously used with people with chronic medical conditions and has been proven effective, without untoward outcomes.

Patient and Public Involvement

The OHP was tailored to long COVID with input from the long COVID clinic clinicians (2 occupational therapists). In addition, guidance was provided on the mode and timing of questionnaire administration with changes made to processes of administration to ensure participants will be prepared and supported. Mindful that the most common symptom of long COVID is fatigue and brain fog, and along with the overall focus of this study (ie, assessing the feasibility and acceptability of LC-OHP), patients with long COVID were not involved in refining the OHP at this stage. However, feedback from patients who used this program in previous studies has been implemented to make the program more succinct, colorful, and visual. Additionally, the delivery of the LC-OHP sessions will be arranged at patients' convenience in terms of time and mode of delivery. Moreover, the views of patient participants who receive the program sessions will be collected by interviewing the pilot participants and the intervention participants at the end of the trial to further implement and adapt the program to people with long COVID. Finally, members of the public will form part of the trial DMC to monitor the progress of the study and contribute to the dissemination of its findings.

Ethics Approval

This study received approval from the University of Suffolk Ethics committee (RETH21/004) and from the NHS Health Research Authority (IRAS 304234).

The study will be conducted in accordance with the Health Research Authority and the University of Suffolk guidelines on ethical conduct in research, as well as the approved study protocol.

Dissemination Plan

The findings of this study will be communicated using different dissemination pathways. These include the use of academic pathways (ie, peer-reviewed journal articles and abstract submissions to local, national, and international conferences), social media pathways (ie, Twitter, YouTube, and LinkedIn), and sending summary findings to participants taking part in this study. The research team will work closely with the DMC, which will include members of the public to identify other appropriate pathways to disseminate the findings to the wider population.

Results

This is an ongoing study, which began in November 2021. The outcomes will be feasibility and acceptability of the program (primary); and its efficacy on improving anxiety, depression, fatigue, self-efficacy, and quality of life (secondary). It is hypothesized that the LC-OHP will be acceptable by participants, will improve their health and psychosocial functioning, and will enable them to gain better understanding of this condition, increasing patient self-efficacy of their symptoms.

Discussion

Principal Findings

In moving this program forward, the feasibility and acceptability of the LC-OHP will be tested along with early measures as to its effectiveness. It is widely acknowledged that long COVID is a chronic condition that is associated with long term, multisystem manifestations. It is a serious health problem that has a significant impact on an individual's physical, social, and psychological functioning. Though there is a good deal of uncertainty and much to be learned about long COVID, there is a pressing need for a specialized intervention to manage the condition.

While the LC-OHP has been used effectively for previous other chronic conditions [58-60,77], it has yet to be used for long COVID. This study has been designed to apply this program to people living with long COVID; however, there is no prior evidence to rely on at present as it is well recognized that COVID and long COVID are new conditions, and researchers and clinicians all over the world are still assessing how best these can be treated. Thus, the program in this study is going to be one of the first and innovative approaches to be used in order to provide additional support to this group of people.

The use of the OHP within this feasibility study offers a holistic approach that can provide a pathway for people to aid them through their recovery and to encourage them to be actively involved in their own management. It uses a person-centered approach and is in line with NICE guidelines and with the NHS plan 2021-22 for managing people with long COVID. It is therefore anticipated that an OHP specifically tailored to patients with long COVID will be acceptable by participants, will have

a high retention rate, will improve their health and psychosocial functioning, and will enable them to gain better understanding of this condition, increasing self-management of their symptoms. This increase in self-management may reduce individuals' contact with health or care services, reducing the demand on the NHS and care services seen during the pandemic. The impact of COVID-19 on mental health is widely acknowledged, and the LC-OHP could be a suitable approach to mitigate this impact and increase individuals' empowerment and independence. Moreover, understanding participants' views and perceptions on the LC-OHP is hoped to improve the program to provide better support for patients with long COVID.

Strengths and Limitations

The study has some limitations. Due to the nature of the intervention, participants and researchers will not be blinded to group allocation; however, to avoid researcher-induced bias, randomization and interviews will be conducted independently.

To the authors' best knowledge, this is the first study to examine an individualized holistic psychosocial program designed to address the needs of adults experiencing long COVID. The study is anticipated to provide evidence for the feasibility and acceptability of the used intervention in improving health outcomes for people experiencing long COVID. This feasibility trial uses a mixed methods design to assess procedural and methodological data in preparation for a fully powered large-scale trial.

Future Directions

The findings of this study will be used in implementing the suggestions given by participants in further adapting and tailoring the LC-OHP program to make it more suitable to people living with long COVID. The findings will also be used as pilot data to support conducting a fully powered large-scale randomized controlled trial to recruit a higher number of participants from multiple sites and from different geographical areas.

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Authors' Contributions

HAJ drafted the manuscript. CFS, KW, DRT, ZMJ, and DJC reviewed and edited the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

In the past 36 months, DJC has received grant money for research from Servier, Boehringer Ingelheim and Travel Support and Honoraria for Talks and Consultancy from Servier, Seqirus, Lundbeck. He is a founder of the Optimal Health Program (OHP) and holds 50% of the IP for OHP. He is also part owner of Clarity Healthcare. He does not knowingly have stocks or shares in any pharmaceutical company. HAJ, KW, DRT, ZMJ, and CFS declare no conflicts of interest.

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Abbreviations

DMC: Data Management Committee
LC-OHP: Long COVID Optimal Health Program
NHS: National Health Service
NICE: National Institute for Health and Care Excellence
OHP: Optimal Health Program
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Implementing Infection Control and Quality of Life Best Practices in Nursing Homes With Project ECHO: Protocol for a Patient-Centered Randomized Controlled Trial

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Abstract

Background: Nursing homes in the United States were devastated by COVID-19, with 710,000 cases and 138,000 deaths nationally through October 2021. Although facilities are required to have infection control staff, only 3% of designated infection preventionists have taken a basic infection control course prior to the COVID-19 pandemic. Most research has focused on infection control in the acute care setting. However, little is known about the implementation of infection control practices and effective interventions in nursing homes. This study utilizes Project ECHO (Extension for Community Health Outcomes), an evidence-based telementoring model, to connect Penn State University subject matter experts with nursing home staff and administrators to proactively support evidence-based infection control guideline implementation.

Objective: Our study seeks to answer the research question of how evidence-based infection control guidelines can be implemented effectively in nursing homes, including comparing the effectiveness of two ECHO-delivered training interventions on key patient-centered outcomes such as reducing the number of residents with a COVID-19 diagnosis.

Methods: A stratified cluster randomized design was utilized. Using a 1:1 ratio, we randomly assigned 136 nursing homes to ECHO or ECHO Plus arms. Randomization was stratified by geographic location, baseline COVID-19 infection rate, and facility capacity. The study had two phases. In phase one, completed in July 2021, nursing homes in both study arms received a 16-week infectious disease and quality improvement training intervention via real-time, interactive videoconferencing and the ECHO learning model. Phase one sessions were up to 90 minutes in duration. In phase two, completed in November 2021, the ECHO group was offered optional 60-minute office hours for 9 weeks and the ECHO Plus group received 9 weeks of 60-minute sessions on emerging topics and an additional 8-session refresher series on infection control.

Results: A total of 290 nursing home facilities were assessed for eligibility, with 136 nursing homes recruited and randomly assigned to ECHO or ECHO Plus. Guided by the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework, we will simultaneously evaluate the study's effectiveness and implementation outcomes at baseline (intervention start date), and at 4, 6, 12, and 18 months. The primary outcome is the COVID-19 infection rate in nursing homes. Secondary outcomes include COVID-19 hospitalizations and deaths, flu-like illness, and quality of life. Surveys and interviews with participants will also provide data as to the adoption, implementation, and maintenance of best practices taught throughout ECHO sessions.

Conclusions: A multipronged approach to improving infection control and emergency preparedness in nursing homes is important, given the toll that the COVID-19 pandemic has taken on residents and staff. The ECHO model has significant strengths

when compared to traditional training, as it allows for remote learning delivered by a multidisciplinary team of experts, and utilizes case discussions that match the context and capacity of nursing homes.

Trial Registration: ClinicalTrials.gov NCT04499391; https://clinicaltrials.gov/ct2/show/NCT04499391

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KEYWORDS

infection control; COVID-19; nursing home; telementoring; Project ECHO; case-based learning; patient-centered outcome; RE-AIM; randomized controlled trial; implementation; quality of life; best practice; guideline; comparison; effectiveness; intervention

Introduction

Nursing homes were ground zero for the COVID-19 pandemic; over half of US nursing home residents were infected (710,000) and 1 in 10 (138,000) died of COVID-19 between March 2020 and October 2021 [1]. The COVID-19 pandemic shines a spotlight on the infection control principles for some of the frailest, most vulnerable individuals in the United States [2]. However, infectious disease outbreaks in nursing homes are not a new challenge, including organisms such as norovirus, influenza virus, and *Streptococcus* [3]. Fortunately, 85.8% of US nursing home residents have been vaccinated against COVID-19, although vaccination alone is not sufficient to prevent outbreaks in the nursing home setting [1].

There are several reasons that infection control within the nursing home setting is a major challenge. Although facilities are required to have designated infection control staff, only 3% had taken a basic infection control course before the COVID pandemic [4-6]. A cross-sectional survey of randomly selected US nursing homes assessed their adherence to the Centers for Medicare and Medicaid Services' (CMS) final rule requiring these facilities to develop an infection control program, employing a trained infection preventionist. One-third of the sample (n=990) reported receiving an infection control deficiency citation [7]. Other challenges to infection control include caregivers moving frequently between rooms, inconsistent hand washing, and vaccine hesitancy [7]. This highlights the need for a multipronged approach to infection control in nursing homes, which is key to battling COVID-19 and future infectious outbreaks in nursing homes.

The Centers for Disease Control and Prevention (CDC) outlines several strategies to assist nursing homes in addressing the pandemic [8]. Unfortunately, these evidence-based infection control practices have failed to translate into effective implementation [9]. Although guidelines may appear relatively straightforward, implementation requires organizational capacity, staff engagement, and problem-solving that can strain organizations lacking appropriate training, resources, and support. Identifying effective implementation for evidence-based practices is of critical importance to decision makers in addressing infection control in nursing homes and requires studying innovative approaches. Although significant research has focused on infection control in the acute care setting, little is known about the implementation of practices and effective interventions in nursing homes [7,10]. A recent systematic review [11] on the effectiveness of preventing or reducing COVID-19 in nursing homes found little evidence linking interventions or strategies to robust data on effectiveness. Most of these studies were observational, with no randomized controlled trials (RCTs) reported to date.

This protocol describes a stratified cluster randomized design to evaluate an intervention utilizing Project ECHO (Extension for Community Health Outcomes), an evidence-based telementoring model to connect Penn State University infectious disease, geriatric, and nursing home experts with remote nursing home staff and administrators to proactively support evidence-based infection control guideline implementation. Our study seeks to answer the research question of how evidence-based infection control guidelines can be implemented effectively in nursing homes. Our primary aim was to compare the effectiveness of a 16-week infectious disease and quality improvement curriculum [12] (ECHO) versus ECHO *plus* a 9-week series on emerging COVID-19 topics and an 8-week infection control refresher series (ECHO Plus) on the number of nursing home residents with COVID-19. Our secondary aims were to compare the effectiveness of ECHO versus ECHO Plus on other patient-centered outcomes (COVID-19 hospitalizations and deaths, flu-like illness, and quality of life [QOL]) and evaluate the impact of intervention conditions on key implementation outcomes in nursing home facilities based on the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework.

Methods

Ethics Approval and Informed Consent

Approval for this study has been obtained from the Penn State Institutional Review Board at the Penn State College of Medicine in Hershey, Pennsylvania (STUDY00015883). All participants received information about the study and were asked to give consent before participating in the study.

Study Design

A stratified cluster randomized design was used. According to a 1:1 ratio, we randomly assigned 136 nursing homes (with approximately 16,700 residents) to ECHO or ECHO Plus. Randomization was stratified by geographic location (rural vs urban), baseline COVID-19 infection rate (some vs none), and facility capacity (<60 beds vs ≥60 beds). Patient-centered outcomes, including nursing home residents with COVID-19 infections, flu-like illness, COVID-19 hospitalizations, deaths, and QOL, were assessed at baseline (intervention start date), and at 4, 6, 12, and 18 months. Our study is guided by the

RE-AIM framework to critically evaluate both effectiveness and implementation outcomes of the proposed cluster RCT [13].

Recruitment

National nursing home lists were obtained using CMS data, state agency and nursing home association contact websites, and engaged stakeholders. We assessed 290 nursing homes for eligibility from national nursing home lists comprising a total of 2000 facilities, focusing primarily in Pennsylvania, but including other states in the Northeast and Midwest, including Connecticut, Delaware, Illinois, Indiana, Maryland, New Hampshire, New Jersey, New York, Ohio, Vermont, Virginia, and Wisconsin. Recruitment occurred from December 2020 to February 2021. In Pennsylvania, nursing homes were recruited through collaborations with key stakeholders, including state agencies and state nursing home organizations, through phone calls and emails. For nursing homes located in other states, we utilized lists obtained from Project ECHO at the University of New Mexico, and made phone calls and sent emails to either the director of nursing or nursing home administrator. Inclusion criteria included being a CMS-eligible facility and no prior participation in a prior ECHO-delivered COVID-19 intervention. Eligible nursing homes were asked to identify two nursing home staff members to participate in the study, and we encouraged participation by infection control staff and other facility leadership (eg, medical director, director of nursing, administrators).

Intervention

The intervention for this study included the Agency for Healthcare Research and Quality (AHRQ) ECHO National Nursing Home COVID-19 Action Network [12], supported by AHRQ and in collaboration with Project ECHO at the University of New Mexico Health Sciences Center and the Institute for Healthcare Improvement (IHI). This network provided training and mentorship to nursing homes across the country to increase the implementation of evidence-based infection prevention and safety practices to protect residents and staff. Using the Project ECHO model of telementoring, all nursing homes received the intervention in two sequential phases from December 2020 to November 2021 (Table 1).

During each session, nursing home staff participated in remote sessions led by a multidisciplinary specialist team consisting of subject matter experts from the following areas of expertise: emergency preparedness, nursing home operations, infectious disease and infection control, geriatrics, mental health, and quality improvement.

To incentivize participation, continuing education credits were awarded for attending live sessions. In addition, a stipend of US $6000 was available through the AHRQ initiative to eligible facilities that participated in or viewed recordings for 13 out of 16 sessions in phase one.

Table 1. Summary of comparators.

Study phase	ECHO[a]	ECHO Plus
Phase one		
16-week infection control ECHO	✓	✓
Quality Improvement component	✓	✓
Phase two		
Nine-week office hours	✓ (optional)	
Nine-week ECHO		✓
Eight-week refresher series (fall 2021)		✓

[a]ECHO: Extension for Community Health Outcomes.

Phase One

Overview

Nursing homes in both study arms received the 16-week AHRQ ECHO National Nursing Home COVID-19 Action Network (Network) curriculum via real-time, interactive videoconferencing using Zoom at no cost to participants. The curriculum was developed specifically for this intervention in partnership between AHRQ, the University of New Mexico's ECHO Institute, and the IHI [12]. Session recordings were available for those who were unable to participate live. Phase one sessions were up to 90 minutes in duration and held weekly for 4 months (16 sessions total) at regularly scheduled times. All sessions followed the required program format for the Network as detailed below.

Introductions

Introductions (5 minutes) provide an inviting atmosphere, with participants including nursing home staff at the frontline in caring for patients and overseeing infection control policies and operations.

Didactic Presentations

Subject matter experts deliver two presentations of 10-15 minutes each on the week's topic (Table 2), including a quality improvement topic delivered by an IHI expert.

Table 2. Phase one curriculum topics.

Week	Topic
1	Preventing and limiting the spread of COVID-19 in nursing homes
2	Infection prevention and management: guidance and practical approaches for use of personal protective equipment during COVID-19
3	COVID-19 vaccine information and rollout
4	Vaccine wrap-up and infection prevention and management: promoting solutions for making the built environment safer, and guidance for cleaning and disinfecting
5	The role of certified nursing assistants in managing and supporting residents and families during COVID-19
6	Managing social isolation during COVID-19: perspectives on staff and residents
7	Infection prevention and management: approaches to cohorting during COVID-19
8	Promoting safe care transitions during COVID-19 –admissions, discharges, and transfers
9	Supporting the emotional well-being of staff caring for residents during COVID-19
10	COVID-19 community transmission and nursing home screening strategies
11	Advance care planning in the time of COVID-19
12	COVID-19 testing for nursing homes
13	Promoting safe visitation and nursing home reopening during COVID-19
14	Staff returning to work safely during COVID-19
15	Interprofessional team management of mild cases of COVID-19
16	Effective leadership and communication during COVID-19

Case Presentations

Typically, each session includes case-based discussions (1-2 cases/session, 30 minutes) to ensure mastery of the content and skills. Each participant presents at least one case during the program. Other participants are encouraged to ask clarifying questions and weigh in on recommendations, followed by ECHO experts who provide advice on addressing each case using best practices. Recommendations are summarized verbally during the session and sent via email. To protect patient confidentiality, cases are presented without protected health information using a standard REDCap case form.

Question and Answer Period

Participants were invited to join an optional question-and-answer session (30 minutes) to further discuss curriculum topics or new challenges in nursing homes.

Close and Debrief

All sessions conclude (5 minutes) with a reminder to complete the session evaluation as provided by the AHRQ, and the subject matter experts encourage participants to put into practice what they have learned, which is later assessed.

Phase Two

The ECHO Plus group received 9 weeks of live 60-minute ECHO sessions instead of office hours, following the format described for phase one and covering emerging topics (Table 3) developed by the research team specifically for this intervention. These topics were identified as timely and important by our stakeholders, subject matter experts, and feedback from participating nursing homes. If nursing home staff were unable to attend the session live, they were offered the recording of that session. In addition, ECHO Plus facilities received an additional 8-session refresher series running from September to November 2021, providing an opportunity to further cover topics that are part of the CDC infection control training and prioritized by our stakeholders and nursing home participants.

The ECHO group was offered the option to participate in phase two of the AHRQ ECHO National Nursing Home COVID-19 Action Network, which consisted of nine weekly 60-minute office hours, in which participants could drop in on an as-needed basis to ask specific questions and receive guidance from our experts on a variety of topics. Although the ECHO group did not receive a brief lecture, we ensured that all session resources shared with the ECHO Plus group, including PowerPoint presentations, were made available to them in a shared online folder.

Table 3. Phase two curriculum topics for ECHO Plus.

Week	Nine-week emerging topic series	Eight-week refresher series
1	COVID-19 variants and vaccine hesitancy	Monoclonal treatment, updates on variants/visitation, flu season and COVID-19
2	Crisis management and communication	Booster updates/new guidelines, vaccines versus natural infection/long COVID, vaccine mandates for staff (impact on staffing), vaccine myths
3	Resident quality of life/social isolation	Navigating and interpreting regulatory and nonregulatory state DOH[a] and federal CMS[b]/CDC[c] guidelines: What is a "must" versus a "should"
4	Grief and loss (for staff, residents, and resident families)	Rounding, audits/checklists, staff onboarding, and training
5	Role of the medical director	Social isolation and grief refresher: trauma-informed care for residents and staff
6	Other staff roles (activities, facilities management, dining/food services)	Occupational Safety and Health Administration compliance training (including volunteers and contractors)
7	COVID-19 updates (information on boosters, new data, new guidance)	Emergency preparedness: now and in the future, nursing facilities as part of US critical infrastructure
8	Sustainability of best practices	Staff and leadership burnout and turnover; institutional knowledge
9	What's next? Ongoing quality Improvement	N/A[d]

[a]DOH: Department of Health.

[b]CMS: Centers for Medicare and Medicaid Services.

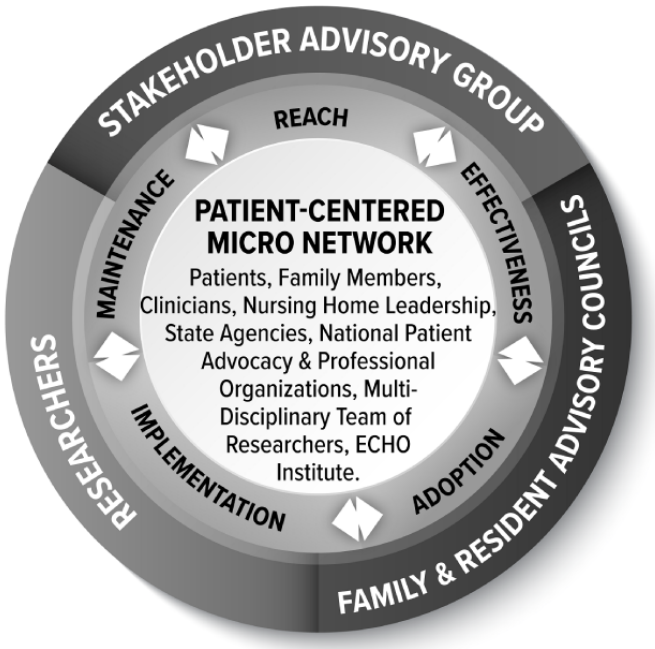
[c]CDC: Centers for Disease Control and Prevention.

[d]N/A: not applicable.

Stakeholder Engagement

We strengthened the patient-centeredness of the study with the addition of a stakeholder advisory board (Figure 1), including engagement on multiple levels in the proposed study's planning and design. The stakeholder advisory board meets every other month, and once annually for a longer meeting, including nursing home patients and their families, nursing home staff/administration, state and federal policymakers, payers, and state professional organizations. These synergistic partnerships across all facets of nursing home care will ensure that our research continually focuses on what matters to stakeholders. We have engaged each of our stakeholders in development of this protocol and their input has shaped the study design. Stakeholders weigh in on important aspects of the study, including recruitment, data collection and analysis, and dissemination.

Figure 1. Patient-centered micro network.



Proposed Outcomes

Guided by the RE-AIM framework [13], we will simultaneously evaluate the study effectiveness and implementation outcomes (Table 4). We will evaluate different aspects of implementation practices in nursing homes. These outcomes will be assessed at baseline (intervention start date), and at 4, 6, 12, and 18 months. These data will be collected using publicly available data sets maintained by federal and state health agencies, validated tools adapted to this project, and interviews with nursing home staff.

The primary outcome is the COVID-19 infection rate in nursing homes (effectiveness). Deidentified patient data will be obtained using the Nursing Home COVID-19 Public File [1] along with three secondary outcomes: flu-like illness, COVID-19 hospitalizations, and deaths. Specifically, the variables that will be assessed include resident weekly and total admissions, resident weekly and total COVID-19 deaths, number of residents with new influenza, and number of residents with acute respiratory illness symptoms excluding COVID-19 and/or influenza. These data are also available for staff. Nursing home resident QOL will be measured using CMS' Minimum Data Set [14], including emotional, symptom and functional statuses, behavioral disturbances, social support, patient engagement, and shared decision-making. CMS data will be linked to participating nursing homes.

Using the RE-AIM framework [13], we will collect several measures to assess how ECHO and ECHO Plus are utilized in nursing homes as implementation outcomes. We will measure reach by assessing the characteristics of nursing homes and staff who participate in the study and those who do not. We will then compare these data to the overall characteristics of nursing homes to assess representativeness. To accomplish this, we will record and categorize participation in each session (eg, number of staff per nursing home site, role of participants in nursing homes, engagement in sessions). At the beginning of each ECHO session, we ask that all participants place their name, email address, and affiliation in the chat box. In addition, we pull Zoom reports to identify participants and the length of time they joined each session (to ensure full participation). We also offer continuing education credits, which is a second opportunity to record engagement and assess quality dimensions that explain participation (eg, satisfaction, acceptability). We evaluate adoption by assessing the characteristics of adopters, as well as barriers and facilitators, using a set of validated instruments adapted to this project, including measures to assess inner and outer contexts of nursing homes [15], the Organizational Readiness for Implementing Change (ORIC) scale [16], the Practice Adaptive Reserve (PAR) scale [17], and the Change Process Capacity Questionnaire (CPCQ) [18].

Table 4. Proposed study outcomes mapped to the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework.

Study outcomes	Description	Data source (timing of assessment)
Reach	Absolute number, proportion, and representativeness of nursing homes and staff who *agree to participate*	Study recruitment logs and staff survey (baseline)
Effectiveness	COVID-19 infection rate (*primary outcome*); flu-like illness, hospitalizations, deaths, quality of life (*secondary outcomes*)	National COVID-19 Nursing Home data file and CMS[a] Minimum Data Set (baseline, 4, 6, 12, 18 months)
Adoption	Absolute number, proportion, and representativeness of nursing homes and staff who *initiate* and *complete* the ECHO[b] series, and barriers and facilitators for adoption	Study participation logs; staff survey (baseline, 6 months) with validated measures, including ORIC[c], PAR[d], and CPCQ[e]; and key informant interviews (6 months)
Implementation	Nursing home staff knowledge and attitudes toward the various intervention functions and components, their level of implementation, and barriers and facilitators for implementation	Selected items from the CDC[f] Preparedness Checklist; staff surveys (baseline, 6, 12 months) with validated measures; and key informant interviews (6 months)
Maintenance	Extent to which implemented guidelines for emergency preparedness in an infectious disease outbreak become part of nursing home policies postintervention	Key informant interviews (12 months)

[a]CMS: Centers for Medicare and Medicaid Services.

[b]ECHO: Extension for Community Health Outcomes.

[c]ORIC: Organizational Readiness for Implementing Change scale.

[d]PAR: Practice Adaptive Reserve scale.

[e]CPCQ: Change Process Capacity Questionnaire.

[f]CDC: Centers for Disease Control and Prevention.

Implementation will be assessed in nursing homes (enactment fidelity) using CDC's COVID-19 Preparedness Checklist [19] for nursing homes as well as barriers and facilitators (ie, Implementation Climate questionnaire, Key Driver Implementation scale) [20]. For maintenance, we will assess policies nursing homes utilize to incorporate best-practice guidelines on addressing COVID-19, quality improvement, and infection control into routine practice. All staff survey data on implementation outcomes will be collected through REDCap. Our implementation evaluation will also include key informant interviews with a subsample of nursing home administrators and staff (n=30) following an explanatory-sequential design. With this design, our team will use interview discussions to further explain the effectiveness results of the study (infection rates, hospitalizations, and deaths) in the words of the implementers themselves, as well as strategies being

implemented to support maintenance. These interviews will also help the study team understand the evolution of contextual factors that were not present at the beginning of the trial (eg, COVID-19 vaccine rollout in nursing home facilities). Main guiding questions (probing questions will be added as needed) are organized under three major themes (Textbox 1).

Textbox 1. Interview guide (6 months).

Theme 1: Experience with COVID-19
Q1. How did the infrastructure of your organization (size, networks, or physical layout) affect the study outcomes?
Q2. Did you have sufficient resources to implement and administer the strategies presented in ECHO sessions?
Q3. Do you consider that the participation of your nursing home facility in the study was a success or a burden? Why?
Theme 2: ECHO Intervention
Q4. How does the intervention compare to other alternatives that may have been considered or that you know about?
Q5. What is your perception on the quality of the ECHO sessions and supporting materials? Did they meet your expectations?
Q6. Tell me a new strategy that your facility implemented in the past 6 months because of participating in this study.
Theme 3: Vaccine Rollout
Q7. Describe your facility's experience with the COVID-19 vaccine rollout. What are you doing to ensure that new residents get vaccinated?
Q8. What is your facility doing to increase vaccine confidence and uptake among staff?

Power Analysis

According to the CMS weekly data as of April 2021, the average weekly COVID-19 infection rate was 0.1%, the average number of residents in nursing homes (cluster size) was around 75-80, and the coefficient of variation of cluster size was approximately 0.76. Assuming a 1% infection rate in the ECHO arm over the 9 weeks when additional topic sessions are provided in the ECHO Plus arm, our study will have 80% power to detect a significant intervention effect if the infection rate is reduced to below 0.3% in the ECHO Plus arm. This calculation was based on a two-sided statistical test of difference between Poisson rates at α=.05 and an intracluster correlation coefficient≤0.01.

Data Analysis

Overview

We will test the effectiveness of the ECHO Plus group by performing both individual-level analyses and cluster-level (nursing homes) analyses following the intention-to-treat principle. All statistical tests will be two-sided, with P<.05 considered statistically significant. We will compare the observed confounders between two study arms and adjust them in the analysis if they are not balanced by design. To account for intracluster correlations within nursing homes, we will use multilevel models such as mixed effects models or marginal models based on the generalized estimating equation (GEE) method to estimate the intervention effect. Outcomes at 6 months will be analyzed using generalized linear models, with an appropriate link function depending on outcome type. The intervention effect on infection risk will be estimated as the odds ratio or incidence rate ratio based on logistic, Poisson, or negative binomial regressions. State and cohort variations will be examined and accounted for using fixed or random effects in the models. Characteristics of residents (eg, age, gender, cognitive function/dementia) and nursing homes (eg, size, quality, baseline infection rate) will be adjusted. Using all measures at baseline, and at 4, 6, 12, and 18 months, we will perform longitudinal analysis to evaluate if the intervention effect changes over time using the same modeling approach but adding additional variables for time and time-by-intervention interaction. Correlations of repeated measures for the same resident will be considered in model estimation.

For cluster-level analyses, since the aggregated outcomes (infection, hospitalization) are rates or proportions between 0 and 1 instead of being binary or count variables, we will use β regression to model them with a logit link function so that the coefficient can be interpreted as a log odds ratio. We will also perform longitudinal analysis for aggregated outcomes based on β regression.

Subgroup Analysis

We hypothesize that the ECHO Plus effect is heterogeneous and expect stronger intervention effects in subgroups without cognitive dysfunction/dementia as well as in those who are younger. Subgroup analysis regarding key participant factors will be performed similarly to examine potential heterogeneity of intervention effects, further tested by interaction analysis. If the data are sufficient, we plan to explore the heterogeneity of the intervention effect on infection rate based on the key participant factors such as age group, gender, dementia, insurance status, and race/ethnicity.

Missing Data

We plan to record and report all reasons for dropout and missing data. Both mixed effects models and marginal models based on GEE methods are valid if the outcome data are missing completely at random. For data missing at random (ie, depends on observed data only), mixed models can still provide valid inference and the weighted GEE methods will be considered to account for this type of missing data. We will also conduct sensitivity analyses to examine the robustness of results to missing data. Multiple imputation methods will be used to address the missing data in the covariates.

Results

We assessed 290 nursing home facilities for eligibility and 136 nursing homes were enrolled and randomly assigned to ECHO or ECHO Plus (Figure 2). Phase one of the study was completed in July 2021 and phase two was completed in November 2021. Only six nursing home facilities dropped out.

Participating nursing home facilities were divided into six cohorts of up to 25 facilities each (Figure 3). This size allowed for maximum engagement in discussions during sessions. Further, as of April 2022, we have completed most interim assessments of primary and secondary outcomes, and we expect to finalize all data collection activities in August 2022, including our primary outcome evaluation at 18 months postintervention.

Figure 2. CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

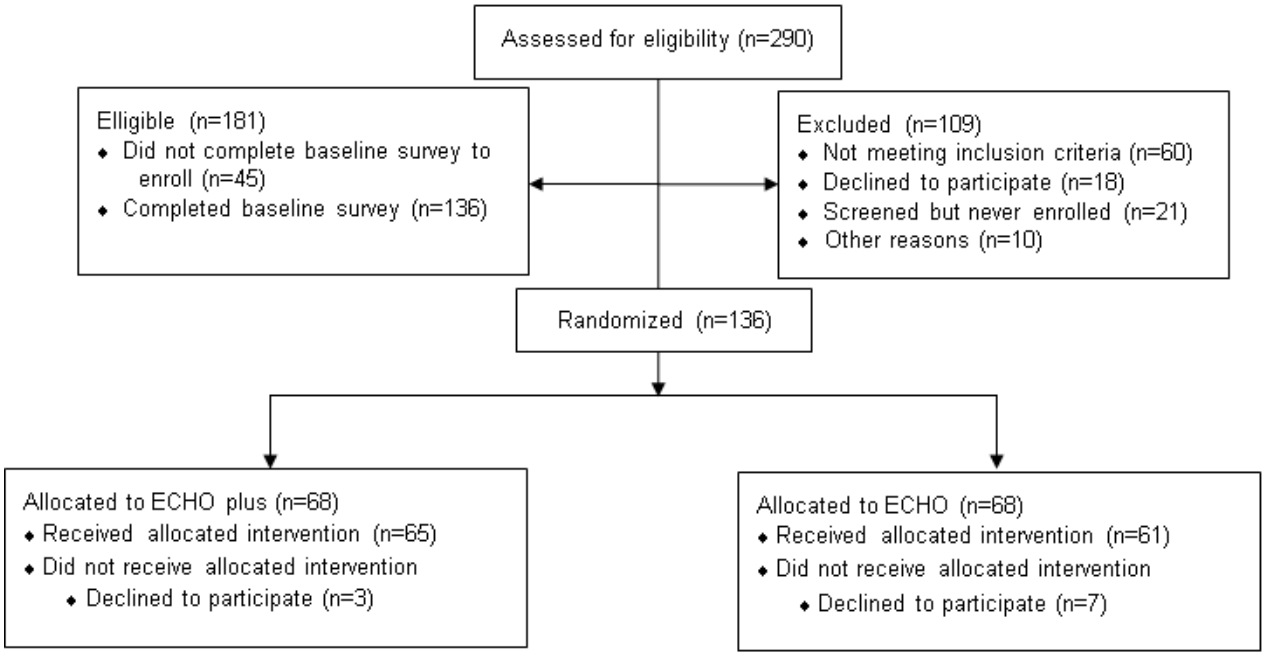
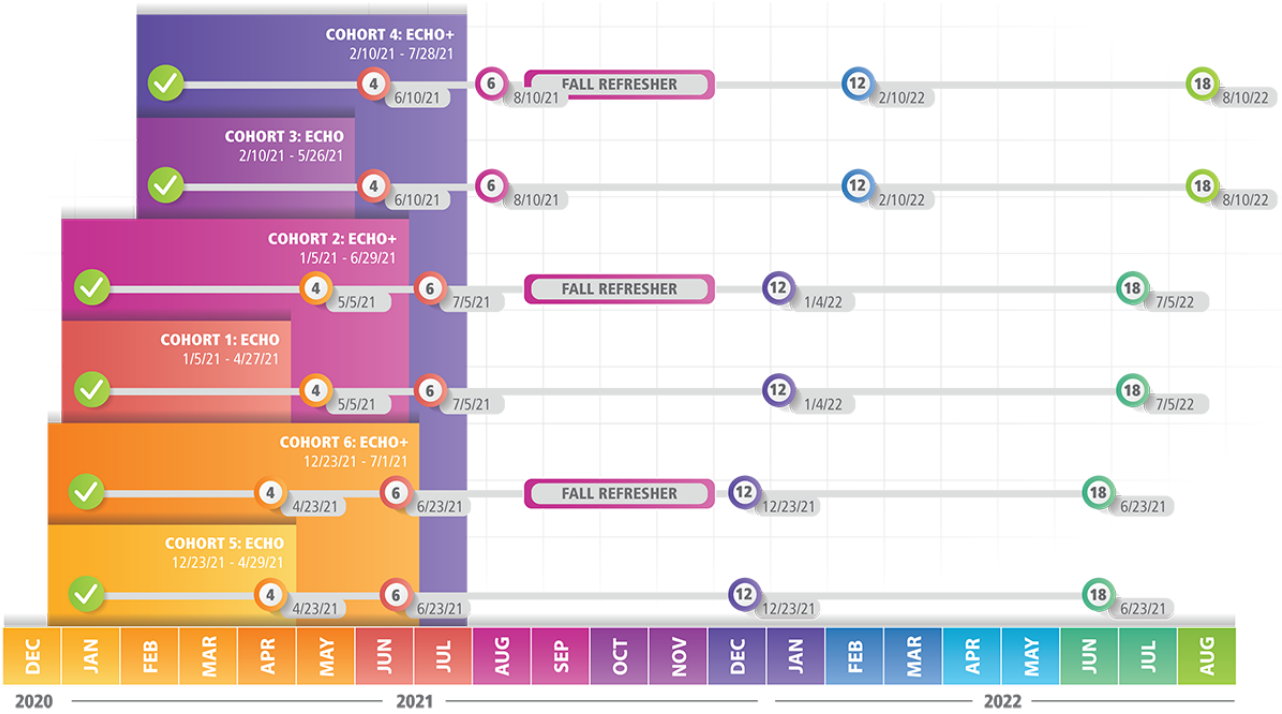


Figure 3. Study timeline.



Discussion

Our study was part of the larger AHRQ ECHO National Nursing Home COVID-19 Action Network. The 136 nursing homes enrolled in our study were among the 9058 sites in all 50 states, the District of Columbia, and Puerto Rico that benefited from no-cost training and mentorship to better protect their residents and staff against COVID-19. All of our intervention activities were completed in November 2021 and we expect to conclude our data collection activities in August 2022, which is 18 months postintervention. We hypothesize that nursing homes engaged in the ECHO Plus intervention will have fewer COVID-19 infections than those in the ECHO intervention after 18 months. Similarly, we hypothesize that nursing home participation in ECHO Plus will significantly improve QOL and decrease COVID-19 hospitalizations and deaths compared to the ECHO intervention.

Although little evidence was available on how to address COVID-19 in nursing homes, our study protocol was informed by formative work we conducted at the beginning of the pandemic. We conducted a needs assessment in April 2020 with nursing home administrators and staff (n=71) that indicated several challenges to implementing infection control strategies, including lack of infection control training, managing resident transfers, preventing transmissions, information overload, and staff well-being. We also launched a pilot COVID-19 ECHO series for health care providers, which engaged 16 nursing homes in Pennsylvania. This formative work demonstrated our team's existing infrastructure and ability to rapidly recruit and engage nursing homes in research studies and provided a critical foundation to this protocol.

If we find our intervention to be effective, we strongly believe this work has great potential for dissemination and implementation. First, we are partnering with the leading institution of the ECHO model, the University of New Mexico, so that our project findings can be easily disseminated across the 240 US institutions offering ECHO. We will also create a dissemination package with curriculum, data collection instruments, and an operations manual to facilitate the use of this project by other ECHO sites. Equally important, this study is disseminable because it was designed using the RE-AIM framework. For instance, understanding aspects of reach, adoption, implementation, and maintenance will assist potential new implementers to assess how amenable the intervention is for their own use. Guided by the RE-AIM framework, we are collecting and evaluating data that are easy to understand and apply in real-world community and clinical settings where research resources are limited. Thus, the RE-AIM framework will greatly strengthen our dissemination capability by providing simplified, pragmatic, user-centered, and theory-driven information to increase the adoption of study findings in additional US nursing home sites.

In conclusion, a multipronged approach to improving infection control and emergency preparedness in nursing homes is critically important, given the toll the COVID-19 pandemic has taken on residents and staff. The ECHO model has significant strengths when compared to traditional training in that it allows for remote learning delivered by a multidisciplinary team of experts, and utilizes case discussions that match the context and capacity of nursing homes. Learners can make real-time changes in practice, as participation equips them to make timely and informed health decisions while leveraging the expertise of specialists during this rapidly evolving pandemic. Understanding how evidence-based infection control guidelines can be implemented effectively in nursing homes is urgently needed, which will have an immediate impact now and for future pandemics.

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Conflicts of Interest

JK served on an advisory board for Sanofi on addressing health disparities in influenza vaccination rates in primary care from October through November 2021. The other authors have no conflicts of interest to declare.

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Abbreviations

AHRQ: Agency for Healthcare Research and Quality
CDC: Centers for Disease Control and Prevention
CMS: Centers for Medicare and Medicaid Services
CPCQ: Change Process Capacity Questionnaire
ECHO: Extension for Community Health Outcomes
GEE: generalized estimating equation
HHS: US Department of Health and Human Services
IHI: Institute for Healthcare Improvement
NIH: National Institutes of Health

ORIC: Organizational Readiness for Implementing Change scale
PAR: Practice Adaptive Reserve scale
PCORI: Patient-Centered Outcomes Research Institute
QOL: quality of life
RCT: randomized controlled trial
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance

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Protocol

Effect of the Nutraceutical Micodigest 2.0 on the Complication Rate of Colorectal Cancer Surgery With Curative Intent: Protocol for a Placebo-Controlled Double-blind Randomized Clinical Trial

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Abstract

Background: Most colorectal cancer patients diagnosed are candidates for surgical resection with curative intent, although colorectal surgery is associated with some complications that could be life-threatening. Antibiotic prophylaxis is commonly used for the prevention of infectious postoperative complications. However, this intervention can change the composition of intestinal microbiota and promote adverse inflammatory outcomes in colorectal cancer patients. The combination of different fungal extracts could be beneficial because of their role in gut microbiota modulation and their anti-inflammatory activity.

Objective: Based on this hypothesis, we have designed a double-bind, randomized clinical trial to evaluate the effect of the nutraceutical fungal extract Micodigest 2.0 on complications of surgery for colorectal cancer resection.

Methods: Colorectal cancer candidates for surgery will be considered for inclusion in the study. After evaluation by the multidisciplinary tumor board, patients who meet selection criteria will be screened, stratified according to tumor location, and randomly allocated to be treated with Micodigest 2.0 or placebo. Treatment will be continued until admission for surgery (4-6 weeks). Participants will undergo a medical and clinical evaluation including baseline and preadmission quality of life, microbiome composition, inflammatory and nutritional status, adverse events, and adherence assessments. The main end point of the study is the surgery complication rate. We will evaluate complications using the Clavien-Dindo classification. It will be necessary to recruit 144 patients to find a relevant clinical difference. We will also evaluate the effect of the nutraceutical on microbiome composition, inflammatory response, nutritional status, and quality of life, as well as the effect of these variables on surgical complications.

Results: This study was funded in 2020 by the Center for Industrial Technology Development. Recruitment began in September 2021 and is expected to be completed in September 2022. Data will be analyzed and the results will be disseminated in 2023.

Conclusions: The results of this protocol study could help to reduce surgery complications in patients with colorectal cancer using the new treatment Micodigest. This study could also identify new features associated with colorectal surgery complications. In summary, this study trial could improve the management of colorectal cancer patients.

Trial Registration: Clinical Trials.gov NCT04821258; https://clinicaltrials.gov/ct2/show/NCT04821258

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KEYWORDS

colorectal cancer; surgery complications; gut microbiota; inflammatory pattern; nutritional status; nutraceutical; postsurgery; colorectal; cancer; colon

Introduction

Colorectal cancer (CRC) is one of the most common malignancies in western countries. In 2018, about half a million cases were diagnosed in Europe, and 250,000 of those affected died due to this disease [1]. Most of the CRCs diagnosed are candidates for surgical resection with curative intent. Cure rates after surgery vary from 92% to 67% depending on the tumor stage [2]. However, colorectal surgery is associated with some life-threatening complications. There are several risk factors associated with these postoperative complications: age, sex, comorbidities, surgery urgency, tumor location, type of surgical approach, and surgical and hospital volume. Postoperative complications are detected during admission in 30% to 40% of patients who have had colorectal surgery [3-6]. Further, one study reported a lower percentage in the month after discharge (15%) and in the first year after surgery (25%) than at other times [3]. The most common complications are anastomotic failure, intra-abdominal infection, prolonged ileus, surgical site infection, deep vein thrombosis, pulmonary complications, and cardiac complications [6]. To assess the severity of surgical complications, different scales are available but the Clavien-Dindo classification is the most used in all parts of the world [7].

Some interventions have been proposed to reduce complications associated with colorectal surgery. Preoperative intravenous antibiotic prophylaxis is commonly used for the prevention of infectious postoperative complications [8]. The most appropriate regimen for antimicrobial prophylaxis for colorectal procedures and the optimal choice of antimicrobial agent have not been fully resolved. However, the last consensus international guidelines on antimicrobial prophylaxis recommend agents with activity against the anaerobic and aerobic floras of the bowel administered within 60 minutes before surgical incision [9]. Studies have shown that oral antibiotic administration can also reduce the risk of infections associated with surgery [10,11]. Other studies, however, have shown that this type of intervention does not modify the mortality and severity of other complications detected [12,13].

In studies analyzing the effect of probiotics, prebiotics, and symbiotics taken prior to the admission on surgery complications, results show that the use of prebiotics reduces the risk of infections associated with surgery and length of stay without affecting other surgery complications or mortality [14]. In addition, in a meta-analysis of 34 randomized clinical trials evaluating the role of probiotics or symbiotics in surgery complications, administration reduced infectious complications during admission without effect on mortality or noninfectious complications [15].

Human intestinal microbiota is a complex ecosystem that maintains homeostasis with the intestine and plays an essential role in wound healing and immune modulation [16,17]. Consequently, microbiota alterations resulting from surgical stress and perioperative management may be associated with the presence of postoperative complications [18]. Mechanical bowel preparation and antibiotic prophylaxis for colorectal surgery have a great impact on the diversity and composition of gut microbiota. It is known that mechanical preparation can both reduce the level of nonpathogenic bacteria like *Bifidobacterium* and *Lactobacillus* and increase pathogenic bacteria like *Escherichia coli* and *Staphylococcus* [19]. Similarly, antibiotic prophylaxis and surgical stress can also impact the gut microbiota by causing changes in diversity and relative abundance [19,20]. Recent studies using animal models have shown substantial alterations in the composition of intestinal microbiota after colon resection [21]. Kong et al [22] evaluated the changes in gut microbiota using fecal samples from 43 CRC patients collected before and after surgery. After CRC surgery, the Bacteroidetes/Firmicutes ratio and the number of obligate anaerobes (including *Bacteroides*, *Bifidobacterium*, *Faecalibacterium*, *Parabacteroides*, and *Prevotella*) decreased [23]. Further, tumor-associated bacteria were eliminated, and butyrate-producing bacteria (*Bacillus*, *Bilophila*, *Barnesiella*) were reduced [23]. On the contrary, conditionally pathogenic bacteria like *Escherichia*, *Shigella*, Enterobacteriaceae, and *Streptococcus* increased [23]. Therefore, alterations of gut microbiota could promote adverse outcome in CRC patients after surgery.

Fungal polysaccharides have attracted attention because of their role in gut microbiota modulation. This type of polysaccharide could reduce pathogen levels and stimulate the growth of beneficial microorganism [24]. As an example, some Basidiomycetes like *Ganoderma lucidum*, *Pleurotus eryngii*, or *Hericium erinaceus* have shown prebiotic activity in animal models [25-27]. In vitro and in vivo studies have shown that polysaccharides from fungi can regulate the microbiota through the fermentation of polysaccharides into short-chain fatty acids [24]. Human studies have also shown a stability for polysaccharides of more than 90% and a capability for stimulating *Lactobacillus* greater than the capability described for other prebiotics [28]. The beneficial effects of fungal polysaccharides is also shown in a randomized study comparing a diet for 10 days based on *Agaricus bisporus* or animal protein. Patients receiving a diet based on fungi showed more Bacteroidetes and fewer Firmicutes [29].

In addition to the beneficial effects of prebiotic activity, fungal polysaccharides have also shown anti-inflammatory activity [27,30]. Polysaccharides isolated from *Ganoderma* and *Lentinula edodes* have shown +immunomodulatory activity in colitis animal models through the production of nitric oxide, tumor necrosis factor alpha (TNF-α), and interleukin-6 (IL-6) [24]. Other examples are the effects of Basidiomycetes extract on the immunological function of inflammatory bowel disease

patients and the ability of *G lucidum* to reduce the levels of pro-inflammatory cytokines in CRC patients [31,32]. In addition, some studies show that a combination of different fungal extracts is necessary to maximize the immunological function of different Basidiomycetes [33,34]. Hence, it seems that this combination could send multiple stimuli to the immune system, increasing intracellular reactions and interactions [35-37].

Micodigest 2.0 (Hifas da Terra) is a nutraceutical, available since 2016, that has had no adverse effects reported. Micodigest 2.0 was designed as a nutritional supplement for cancer patients. It is sold directly to the consumer for approximately 300€ (US $325.88) without a prescription from a health care professional. Micodigest 2.0 comprises 9 fungal extracts: *G lucidum*, *A blazei*, *Grifola frondosa*, *H erinaceus*, *Cordyceps sinensis*, *Inonotus obliquus*, *P ostreatus*, and *Polyporus umbellatus*. Taking into account the beneficial effects of fungal polysaccharides, we hypothesized that the fungal extract nutraceutical Micodigest 2.0 could be used to reduce complications after CRC surgery with curative intent.

For these reasons, we have designed a double-blind randomized clinical trial to evaluate the effect of Micodigest 2.0 on complications after surgery with curative intent for CRC. Apart from this purpose, we have also set the following secondary objectives:

- Evaluate the safety of Micodigest 2.0 in CRC patients
- Evaluate the effect of Micodigest 2.0 on fecal microbiome composition and diversity
- Evaluate the effect of Micodigest 2.0 on inflammatory pattern, nutrition status, and quality of life
- Analyze the effect of the microbiome, inflammatory pattern, and nutrition status on complications after surgery

Methods

Study Design

We designed this study as a randomized, double-blind clinical trial. The study will be conducted in the gastroenterology department of Hospital Universitario de Ourense, Ourense, Spain. CRC candidates for surgery with curative intent will be considered for inclusion in the study. Patients who meet the criteria will be screened and randomly allocated to be treated with Micodigest 2.0 or placebo previous to admission. Additionally, we will stratify the included patients based on tumor location (distal or proximal to splenic flexure). The protocol includes a follow-up period of 4 to 6 weeks before surgery. This study has been developed in line with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [38].

Ethics Approval and Consent to Participate

The study has been designed according to the Declaration of Helsinki and the latest Good Clinical Practice guidelines. Ethical approval was obtained from the clinical research ethics committee of Galicia, Spain (2021/ 036), and the study was registered at ClinicalTrials.gov [NCT04821258].

Informed consent will be obtained from all study participants. Any possible protocol modification will be communicated to the ethical committee and all relevant parties. The staff study members will inform participants that they can withdraw their consent to participate at any time and for any reason. Additionally, all study patients will receive an information sheet that will include objectives; methodology; interventions; action to be taken in case of forgetting treatment dose; benefits, risks, and possible adverse events; voluntary participation and right to withdraw; confidentiality; action to be taken with the remaining treatment at the end of the study; and information about the principal investigator. A trained medical doctor will provide these documents at the first visit.

Inclusion Criteria

CRC patients will be aged 18 to 85 years, be a candidate for surgical treatment with curative intent (stage I-III), have an American Society of Anesthesiologists physical status classification of I or II and a score between 0 and 2 on the Eastern Cooperative Oncology Group scale, understand the information and make decision themselves (with preserved cognitive function), and provide authorization after reading the study information sheet.

Exclusion Criteria

Patients who are candidates for neoadjuvant therapy, have concomitant carcinoma (carcinoma diagnosed in a person who has previously experienced another cancer at any time), are allergic to the supplied nutraceutical or previous medical diagnosis of malabsorption syndrome, have a mental disorder that can cause the loss of cognitive function, have active infection or have taken antibiotic therapy in the last month, or have had previous colectomy surgery will be excluded from the study.

Intervention

Patients will be randomized into 2 treatment groups: arm A (control) patients will be treated with placebo before surgery in the same way and timing as the nutraceutical and arm B (experimental) patients will be treated with Micodigest 2.0 before surgery.

The Hifas da Terra company will provide Micodigest 2.0 as 30 capsules and 300 mL syrup with a syringe to measure doses. The drinkable syrup consists of organic extracts from *G lucidum*, *A blazei*, *G frondosa*, *H erinaceus*, *Pleutorus eryngii*, *P ostreatus*, *Myrciaria dubia*, and purified water, raw agave, and natural aroma. The clear vegetable capsules contain *Levilactobacillus brevis*, *Lactiplantibacillus plantarum*, magnesium stearate, silicon dioxide, and extract from *G lucidum*. This treatment is a dietary supplement that has been available since 2016; no adverse effects have been reported. The treatment dose will initiate with 10 mL/day and 1 capsule/day (before breakfast or before lunch) for 7 days and increase to 20 mL/day and 2 capsules/day (10 mL + 1 capsule before breakfast and 10 mL + 1 capsule before dinner) until surgery admission (4-6 weeks).

In the same way, the Hifas da Terra company will supply placebo as 30 capsules and 300 mL syrup with a syringe to measure doses. The drinkable syrup consists of purified water, natural aroma, and agave nectar. This syrup also includes peptin

and guar gums as gelling agents and potassium sorbate as preservative. The capsules contain hydroxypropyl methylcellulose and silicon dioxide as anticaking agents and microcrystalline cellulose as a gelling agent. The treatment dose will initiate with 10 mL/day and 1 capsule/day (before breakfast or before lunch) for 7 days and increase to 20 mL/day and 2 capsules/day (10 mL + 1 capsule before breakfast and 10 mL + 1 capsule before dinner) until surgery admission (4-6 weeks).

The assigned study intervention will end if allergic reactions or any serious adverse events are reported. Additionally, patient withdrawal will be a criteria for discontinuing any intervention.

Randomization

We will randomize into the 2 parallel treatment arms using the distribution of a blinded treatment kit containing test or placebo supplementation. We will perform randomization using a code list randomly created using R software (R Foundation for Statistical Computing). This code list will include a total of 144 random numbers. Each random number will match with a unique identification code that will identify test or placebo. The randomization will ensure an equal sample size for each group. The dietary supplement will be randomly assigned into the test or placebo groups at a 1:1 ratio according to the random numbers generated.

Blinding

This is a double-bind clinical study, so the patient and trial staff will not know the arm of allocation. The trial staff will prepare treatment kits by assigning them the identification codes following the randomization list. The kits will look exactly the same, with the name of the company, name of the drug, and information about how to take the treatment. The kit code will be identified by the principal investigator of the study only if needed for the safety of the patients.

Preoperative Nutritional Supplementation

Nutritional supplementation will be carried out based on the risk of malnutrition and independently of the study protocol. To identify those at risk of malnutrition, a Patient-Generated Subjective Global Assessment (PG-SGA) will be completed by the patient [39]. In case of moderate or severe malnutrition, we will refer patients to nutrition consultation. Patients referred to nutrition consultation will also complete the treatment during the follow-up period before surgery (4-6 weeks).

Sample Size

We designed the study on the basis that the complication rate in the nonintervention arm is 40% and that a 50% reduction would be clinically relevant. Assuming a β error of .80 and an error of .05, 64 patients should be included in each arm. Accounting for a dropout rate of 10%, it would be necessary to include a total of 144 patients (72 patients in each group). The sample size calculation was performed with the Ene 3.0 (GlaxoSmithKline SA) statistical software. A medical doctor will explain the benefits of participating in the study to the patients at the digestive oncology consultation to reach the target sample size.

Study Period

A participant's involvement in the study will end after 4 to 6 weeks. The schedule of this study will include enrollment, allocation, weekly phone call, and closeout visit at the time of patient admission (Table 1). We will also collect information after patient discharge.

Table 1. Study schedule for clinical study visits.

Time point	Study period				
	Visit 0	Visit 1	Follow-up	Closeout	Discharge
Enrollment					
Selection criteria review	✓				
Informed consent	✓	✓			
ID number	✓				
Randomization		✓			
Intervention					
Arm A (placebo)		✓			
Arm B (experimental)		✓			
Compliance			✓	✓	
Assessment					
Nutritional evaluation		✓		✓	
Quality of life		✓		✓	
Medical history		✓			✓
Complication rate (Clavien-Dindo)					✓
Adverse effects			✓	✓	
Fecal and blood sample collection		✓		✓	

At visit 0, we will review inclusion and exclusion criteria. Patients who meet the criteria will be informed about the study and assigned an ID number. The principal investigator will record and keep this number appropriately. Patient will receive the informed consent and a device to collect a fecal sample at home.

At visit 1 (baseline), if patient agrees to participate in the study, we will perform randomization. We will also evaluate nutritional status and perform the quality of life assessment. Previous medical history will be recorded, fecal sample will be obtained from the patient, and blood samples will be collected. If malnutrition is detected, we will refer the patient to nutrition consultation. Additionally, the patient will receive another device to collect the needed fecal sample at the end of the study.

Follow-up visits will be performed weekly for 4 to 6 weeks. We will use this weekly phone call to collect data about adverse effects and treatment compliance.

Closeout visit will be done at the same time as patient admission. The intervention will end at this time, and patients will return the remaining treatment to researchers. We will also pick up fecal and blood samples, evaluate the nutritional status, and assess quality of life again. Further, data about adverse effects will be collected.

The end of the study will be defined by patient discharge. We will evaluate and classify the surgery complications at this time. Data collection will include information about antibiotic prophylaxis used, length of stay, vital status, surgery performed, and final staging of the CRC according to the TNM.

Outcomes and Data Collection

Medical History

Data regarding inclusion and exclusion criteria, demographic variables, tumor location, tumor stage, and type and duration of symptoms will be collected at first visit. At the time of patient discharge, we will also recover data about type of surgery, length of stay, vital status, type of surgery complications, and stratification of postoperative complications according to the 5 categories in the Clavien-Dindo classification.

Nutritional Evaluation

We will use 4 anthropometric measures to evaluate nutritional status: weight, height, BMI, and body fat percentage. Nutritional status assessment will be based on the PG-SGA survey and albumin, prealbumin, total lymphocytes, and hemoglobin levels.

Quality of Life

We will use the 36-item Short Form Health Survey to evaluate the quality of life. This survey has been validated and is frequently used to assess quality of life in CRC patients [40].

Treatment Compliance

A staff study member will deliver treatment for 6 weeks at the baseline visit. The researchers will ask about compliance and quantity of treatment used at follow-up visits. Patient will return the remaining treatment at closeout visit. This delivery option has been proposed to minimize visits to the hospital and promote retention and completion of follow-up.

Adverse Effects

Adverse events and their severity will be collected using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [41]. The principal investigator will be responsible for reporting adverse effects of interest and serious events to the sponsor. The sponsor must immediately report possible serious events that may be related to the treatment.

Blood Samples

Blood samples will be collected at baseline and closeout visits. These samples will be stored at –20 ˚C until analysis. Laboratory analysis will include hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, albumin, prealbumin, C-reactive protein, creatinine, prothrombin time, neutrophil-lymphocyte ratio, IL-6, IL-10, and TNF-α levels.

Fecal Samples

Fecal samples will be collect at baseline and closeout visits. Patient will collect the samples at home and deliver them to the clinic within 4 hours of collection. Again, samples will be frozen at –20 ˚C until analysis. Fecal sample analysis will start with a high-quality DNA extraction. The analysis will continue with the bacterial 16S ribosomal RNA gene being sequenced on a MiSeq benchtop sequencer (Illumina Inc). Finally, microbiome composition will be defined using metagenomic species and a database with >200,000 strains.

Data Management

We will collect all the data in an electronic data notebook. Additionally, the principal investigator will keep a copy of all these data to ensure data entry security. Data integrity will be enforced using data rules and checks applied at the time of data entry. Moreover, all the modifications to the data will be documented. A missing visit will not imply a loss to follow-up. The principal investigator and all staff members responsible for data collection and data analysis will have access to the final trial data set.

Data Confidentiality

The trial staff will depersonalize all the information related to patients and keep these data anonymous. Moreover, the results of the study will always be presented globally in order to preserve the confidentiality of the data. The promoter, Fundación Biomédica Galicia Sur, will obtain clinical trial insurance to cover any physical injury or damage to property that may occur during the study. This clinical trial insurance will also provide coverage for the promoter, researcher, collaborators, and head of the center where the study is performed.

Statistical Analysis

Descriptive Statistics

Descriptive analysis will be performed with SPSS (version 24.0, IBM Corp) statistical software. We will use frequency and percentage to describe qualitative variables and median and interquartile range to describe quantitative variables.

Inferential Statistics

We will apply inferential statistics to identify differences between the control and experimental groups. In general,

dichotomous variables will be compared with chi-square tests, whereas qualitative variables with more than 2 categories will be compared with analysis of variance tests. Continuous variables will be compared with *t* tests for independent samples or Mann-Whitney *U* tests if they do not meet normality. $P<.05$ will be considered statistically significant. More specifically, to analyze the outcomes of the study the following statistical methodology will be performed:

- We will analyze the complication rate after surgery in the 2 intervention groups. We will base this analysis on severity and type of complication. After stratification by tumor location, we will use chi-square tests to identify significant differences between the 2 groups. Risk ratio and 95% confidence interval will be used to describe the differences found.
- We will describe adverse events reported in each group. To find significant differences between the 2 groups, chi-square tests will be used after stratification by tumor location. Risk ratio and 95% confidence interval will be used to describe the differences found.
- Diversity and composition of the gut microbiota will be analyzed in the 2 groups using McNemar tests and *t* tests to identify significant differences between the groups.
- Inflammatory differences between the 2 intervention groups will be analyzed with *t* tests if variables meet normality or Wilcoxon tests if variables do not meet normality. We will also analyze the dynamic changes of the neutrophil-lymphocyte ratio in the 2 intervention groups.
- Differences in dietary pattern and quality of life will be analyzed with McNemar tests for qualitative variables and *t* tests for quantitative data.
- We will perform a univariate analysis to identify any associations between impact of the microbiome, inflammatory and dietary patterns, and surgery complications. We will perform a multivariate regression with the significant variables found. In addition, the model fit will be assessed using a likelihood-ratio test, area under the receiver operating characteristic curve, Akaike information criterion, and Bayesian information criterion, and we will then validate the model designed using the bootstrap method.

Finally, we will perform a causal mediation analysis to measure the direct and indirect effects of Micodigest 2.0 on colorectal surgery complications. We will include as mediators the variables related to complications after surgery. This analysis will also show the total effect of other variables on colorectal surgery complications.

Results

This study was funded in 2020 by the Center for Industrial Technology Development with the project “Research on the modulation of microbiota and its effects on biomarkers associated with well-being and health (2/3).” Patient recruitment began in September 2021, with completion tentatively set for September 2022. We expect to complete the analysis, publish the results in local and international journals, and present the study findings at conferences and clinical meetings in 2023.

Discussion

Principal Findings

The trial has been designed to evaluate the effects of a new dietary supplement on complications associated with surgery in CRC patients. The results, if positive, may provide a change in the current guidelines for preoperative care in CRC. Additionally, this study protocol will confirm the safety of the Micodigest 2.0 supplement and evaluate patient adherence to this new treatment. In sum, the results may provide a simple, safe, and inexpensive intervention with good adherence rates to reduce surgery complications and consequently improve the quality of life of CRC patients.

The protocol is necessary not only to study the effects of Micodigest 2.0 but also to investigate patterns and features related to complications after surgery. The results may show clinical features, inflammatory patterns, or nutritional statuses associated with postoperative complications. Moreover, the results could show new effects of gut microbiota on surgery complications. Therefore, the protocol could identify risk factors for postoperative complications and contribute to the design of new clinical studies to prevent CRC surgery complications.

Interest in the role of fungal polysaccharides in gut microbiota and immune regulation has increased in recent years. The results of this study may improve the knowledge about the biological functions of fungal polysaccharides. Further, this trial may help to define new health benefits of these bioactive polysaccharides and design new studies on their use in CRC patients. Hence, the use of fungal polysaccharides as probiotics could introduce a new step in the prevention and treatment of CRC. Bioactive polysaccharides may improve the response to treatment, especially immunotherapies, due to their immunomodulating activity. These polysaccharides could also increase the safety of treatments commonly used in cancer and alleviate adverse effects of these therapies. Additionally, the anti-inflammatory activity of fungal polysaccharides could influence carcinogenesis, progression, and tumor metastasis.

Limitations

A potential limitation of our study is the risk of loss to follow-up. Remarkably, the loss to follow-up could be different for one of the exposure outcome categories. In consequence, the measure of association will be biased. Additionally, nonadherence to the treatment could be another potential limitation of our clinical trial. Hence, some subject will fail to adhere to the protocol, and nonadherence will cause an underestimated measure of association.

Conclusion

In summary, this clinical trial may provide a safe and effective treatment for CRC surgery complications and contribute to new study designs for the management of CRC surgery candidates for resection with curative intent.

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Authors' Contributions

CR participated in the study design and drafted the manuscript. JC developed the study design and contributed to drafting the manuscript. LC participated in the study design. LGN participated in the study design and was responsible for clinical laboratory analysis. SZ and DR participated in the study design and supervised the clinical protocol. ARB, ES, and CFA participated in the study design and were responsible for providing treatments. All authors approved the final version of this manuscript.

Conflicts of Interest

CFA belongs to the research and development team of Hifas da Terra.

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Abbreviations

CRC: colorectal cancer
CTCAE: Common Terminology Criteria for Adverse Events
IL-6: interleukin-6
PG-SGA: Patient-Generated Subjective Global Assessment
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TNF-α: tumor necrosis factor alpha

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Protocol

Efficacy of Ibuprofen Gargle for Postoperative Pain After Mandibular Third Molar Extraction: Protocol for a Phase II, Placebo-Controlled, Double-Blind, Randomized Crossover Trial

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Abstract

Background: Extraction of mandibular third molars is one of the most commonly performed oral surgical procedures, and nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for pain management. Oral NSAIDs are associated with adverse events such as gastrointestinal disorders, renal and hepatic dysfunction, and platelet dysfunction. Topical analgesics have been proposed as alternatives to oral and injectable medications to safely improve postoperative pain relief. We will conduct a single-center, placebo-controlled, double-blind, randomized crossover trial to assess the pain-relieving effect of an ibuprofen-containing gargle in patients undergoing extraction of mandibular third molars when compared with a placebo gargle.

Objective: This will be the first clinical study to compare the efficacy of an ibuprofen gargle with that of a placebo for relieving postoperative pain in addition to loxoprofen after mandibular third molar extraction.

Methods: This study will be performed at Kobe University Hospital. Participants (N=40) will be randomized equally to 1 of 2 groups. The ibuprofen-placebo group will receive an ibuprofen gargle on postoperative day (POD) 1 and a placebo gargle on POD 2. The placebo-ibuprofen group will receive a placebo gargle on POD 1 and an ibuprofen gargle on POD 2. Both groups will receive ibuprofen gargles on PODs 3-5 at least once daily. The primary objective is to estimate the within-subject difference on a visual analog scale (VAS) before and 5 minutes after using the ibuprofen or placebo gargle on PODs 1 and 2. The secondary objectives are to estimate the within-subject differences in ΔVAS before and 15 minutes after using the ibuprofen or placebo gargle on PODs 1 and 2, ΔVAS before and 5 or 15 minutes after using the ibuprofen gargle on PODs 3-5, overall efficacy (self-completion, 5 scales) on PODs 1-5, daily frequency of use (ibuprofen or placebo gargle and analgesics) on PODs 1-7, and the occurrence of adverse events.

Results: The Certified Review Board of Kobe University approved the study. The intervention was implemented in May 2021. For the primary analysis, we will calculate the mean and SD of ΔVAS_5 on PODs 1 and 2 and the within-study difference in ΔVAS_5. The treatment effect will be estimated by dividing the mean ΔVAS_5 in the within-subject difference by 2 and calculating the *P* value using an unpaired *t* test. For the secondary analysis, we will calculate the mean and SD of ΔVAS_{15} on PODs 1 and 2 and the within-study difference in ΔVAS_{15}. The treatment effect will be estimated as in the primary analysis.

Conclusions: This trial will provide exploratory evidence of the efficacy and safety of an ibuprofen gargle for pain reduction after mandibular third molar extraction.

Trial Registration: Japan Registry of Clinical Trials jRCTs051210022; https://tinyurl.com/39ej23zu

International Registered Report Identifier (IRRID): DERR1-10.2196/35533

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KEYWORDS

protocol; phase II; placebo-controlled; double-blind; randomized crossover trial; mandibular third molar extraction; pain management; ibuprofen; gargle

Introduction

Extraction of the mandibular third molar is one of the most commonly performed oral surgical procedures [1,2]. Because of the high degree of invasiveness when bone removal and crown division are involved, moderate to severe postoperative complications may occur, such as pain, swelling, difficulty in mouth opening and swallowing [2,3], and postoperative difficulty in oral intake.

Postextraction pain is one of the most common and important postoperative complications after dental extractions, and it is the reason many patients avoid treatment [1]. Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen are the accepted analgesics for the treatment of postextraction pain [4], and acidic NSAIDs are usually chosen for moderate pain, such as that with mandibular extractions. In patients with gastrointestinal ulcers or aspirin-induced asthma, acetaminophen may be used as an alternative drug [4]. NSAIDs, such as celecoxib [5,6], valdecoxib [7], ibuprofen [8], flurbiprofen [9], lornoxicam [10], etoricoxib [11], and opioid-containing drugs such as oxycodone [12] have been studied to identify the optimal analgesics for pain relief in mandibular third molar extractions. In a systematic review of 21 high-quality clinical trials, Weil et al reported that oral paracetamol (acetaminophen) was safe and effective in the treatment of postoperative pain after extraction of embedded mandibular third molars [13], and in a Cochrane review of 2242 patients, Bailey et al reported that oral ibuprofen was superior to oral paracetamol in the treatment of postoperative pain [14].

Side effects should be considered when prescribing analgesics in the postoperative period, with opioids mainly associated with respiratory depression, nausea and vomiting, and constipation [15], and NSAIDs mainly associated with gastrointestinal disorders, renal and hepatic dysfunction, and platelet dysfunction [16]. To address the problems associated with opioid use, Rindal et al [17] recently published the protocol for a randomized controlled trial of interventions to decrease the prescription of opioids in favor of nonopioid drugs. Additionally, topical use of analgesics has been proposed as an alternative to oral and injectable medications to safely improve postoperative pain relief [9,18,19]. Topical administration has also been reported to reduce side effects without reducing the quality of analgesia [20].

Ibuprofen, developed in the 1960s, is a potent inhibitor of prostaglandin synthesis and reduces fever, pain, and inflammation [21]. Because ibuprofen is pharmacologically active against cyclooxygenase-1 and cyclooxygenase-2, adverse effects such as gastrointestinal and renal dysfunction may occur after systemic administration. However, several reviews and meta-analyses have shown that ibuprofen is effective in adults and children and is the least toxic of the NSAIDs [22-24]. We hypothesized that an oral gargle containing dissolved ibuprofen (0.6% or 1%) delivered directly to the affected area could contribute to pain relief for oral mucositis. In our previous study, we have reported that there are no major safety concerns and that some pain relief is obtained for chemotherapy- or chemoradiotherapy-associated oral mucositis [25].

In postextraction wounds, the loss of keratinized mucosa associated with tooth extraction allows for rapid absorption and efficacy of topically administered medication in the affected area [26]. It is hoped that ibuprofen-containing gargles will provide an efficient drug delivery system targeting the painful area after tooth extraction, with minimal systemic effects. An unresolved limitation of our previous study [25] is that it was not possible to estimate the extent to which a placebo effect may have been present because the study was an uncontrolled trial involving healthy adults and patients with chemotherapy- or chemoradiotherapy-associated oral mucositis [25].

The aim of this clinical study is to evaluate the efficacy and safety of an ibuprofen gargle for relieving postoperative pain in patients with extracted mandibular third molars to assess whether the pain-relieving effect of an ibuprofen gargle can be confirmed without compromising the quality of postextraction pain management in daily practice. To our knowledge, the use of an ibuprofen gargle instead of a placebo for supplemental postoperative pain relief after third molar extractions has not been evaluated previously.

Methods

Ethics Approval

The study will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of good clinical practice, and all the applicable regulatory requirements. Ethics approval was provided by the Clinical Research Ethics Committee at Kobe University (reference number: C200024). The trial was registered on the Japan Registry of Clinical Trials (trial registration: jRCTs051210022).

Consent to Participate

Written informed consent will be obtained from all participants before any study procedure is performed. The participants will have the opportunity to review the consent form and confirm that they fully understand the details of the study procedures. Informed consent will be administered by a suitably qualified and experienced individual who has been assigned this duty by the principal investigator. Secondary use of the data will occur only if the patients provide written informed consent for additional use of their data.

Primary Objective

The primary objective is to estimate the within-subject difference on a visual analog scale (VAS) that ranges from 0

(no pain) to 10 (worst pain) continuously immediately before and 5 minutes after the use of an ibuprofen or placebo gargle on postoperative days (PODs) 1 and 2 in patients undergoing mandibular third molar extractions (ΔVAS_5_ibuprofen − ΔVAS_5_placebo).

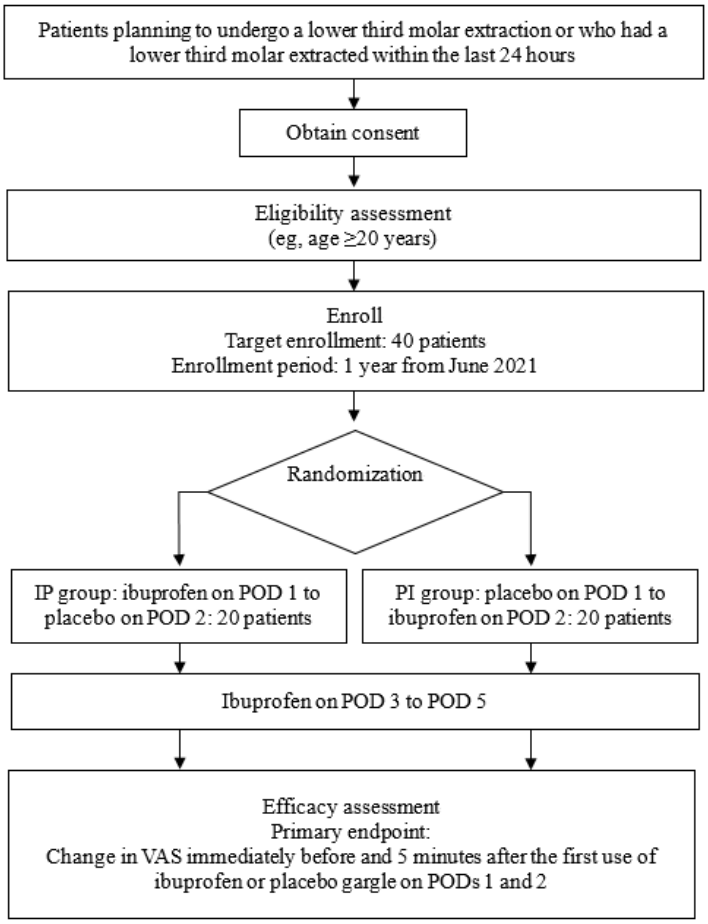
Secondary Objectives

The secondary objectives are to evaluate the within-subject difference in ΔVAS 15 minutes before and 15 minutes after use of an ibuprofen or placebo gargle (ΔVAS_{15}_ibuprofen − ΔVAS_{15}_placebo) on PODs 1 and 2, the ΔVAS before and after 5 or 15 minutes of the use of an ibuprofen gargle on PODs 3-5, the overall efficacy (self-completion, 5 scales) on PODs 1-5, the daily frequency of use (ibuprofen or placebo gargle and analgesics) on PODs 1-7, and the occurrence of adverse events.

Study Design, Setting, and Population

This study is designed as a single-center, placebo-controlled, double-blind, randomized crossover trial. The patient flowchart is shown in Figure 1. This study will be performed at Kobe University Hospital. All study data will be stored and archived in the data center at Kobe University Hospital. We will use Research Electronic Data Capture (REDCap), which is an electronic data system for clinical research, to manage the data and protect confidentiality before, during, and after the trial. The study population will comprise patients who undergo third molar extraction and will be selected based on the inclusion and exclusion criteria given in Textbox 1. All patients undergoing third molar extraction during the study period (June 1, 2021, to September 30, 2022 [expected end date]) will be provided with information about the study. All patients will be asked if they wish to participate in the study and will be enrolled after obtaining written informed consent.

Figure 1. Flowchart of the study design. IP: Ibuprofen-Placebo; PI: Placebo-Ibuprofen; POD: postoperative day; VAS: visual analog scale.



Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Patients planning to have a mandibular third molar extraction or who have had a mandibular third molar extracted within the last 24 hours
- Patients aged 20 years or older at the time of consent acquisition
- Patients for whom documented consent has been obtained regarding their voluntary participation in this clinical study

Exclusion criteria

- Patients with peptic ulcers
- Patients with concurrent severe or uncontrolled concomitant medical conditions
- Patients with a history of hypersensitivity to any component of the ibuprofen gargle
- Patients with impaired cardiac function or clinically significant heart disease
- Patients with aspirin-induced asthma
- Patients who use analgesic drugs at least once a week for any chronic pain
- Patients with dementia, psychiatric symptoms, drug addiction, or alcoholism
- Pregnant or lactating women
- Patients deemed inappropriate (for miscellaneous reasons) based on the assessment of the investigator or the subinvestigator

Surgical Procedure and Prohibited Interventions

All surgeries should be performed by an experienced oral surgeon with a minimum of 3 years of postgraduate experience using the same protocol. Povidone iodine solution will be applied inside the mouth, and 2% lidocaine + 1:80,000 epinephrine carpules will be used to block the inferior alveolar nerves by injection. A mucoperiosteal envelope flap will be created using a standard incision. If needed, bone removal and tooth sectioning will be performed with a low-speed hand piece under sufficient sterile solution irrigation. Following tooth removal, the socket will be irrigated with 10-20 mL of saline, and the flap will be sutured using 2-3 resorbable sutures (3–0 Vicryl; Ethicon Inc). The operation time will be recorded in minutes from the time of incision to the completion of the last suture. If needed, supplementary intraoperative local analgesia will be administered and recorded. Loxoprofen (60 mg) will be prescribed postoperatively, and the patients will be instructed to take up to 3 tablets daily for pain. The dosing information will be recorded in the patient diary with the number of analgesics used per day for up to 10 days postoperation. Antibiotics will be prescribed postoperatively and will be administered up to POD 2. Patients will be prescribed 1 loxoprofen sodium tablet (60 mg) daily and the ibuprofen and placebo gargles as part of the study protocol. The use of other analgesics, such as opioids and other NSAIDs, is prohibited.

Ibuprofen and Placebo Gargle Intervention and Treatment Protocol

The ibuprofen gargle is manufactured at the Department of Pharmacy, Kobe University Hospital. The gargle (100 mL) contains ibuprofen 600 mg (0.6%), sodium hydroxide, sodium hydrogen carbonate, hydrochloric acid (to regulate pH), glycerin, and flavor. The placebo gargle formulation is the same but without ibuprofen. The intervention or treatment protocol will be as follows: (1) ibuprofen-placebo (IP) group prescribed with ibuprofen gargle on POD 1, placebo gargle on POD 2, and ibuprofen gargle on PODs 3-5 at least once daily and (2) placebo-ibuprofen (PI) group prescribe with placebo gargle on POD 1, ibuprofen gargle on POD 2, and ibuprofen gargle on PODs 3-5 at least once daily.

As for the dosage, approximately 10 mL of gargle solution is dispensed into a measuring cup and retained in the mouth in contact with the affected area for at least 30 seconds (preferably 1 minute), and it is then discarded.

Patients will not drink water or rinse their mouths for at least 5 minutes after using the gargle.

As a general rule, patients will be allowed an interval of at least 15 minutes between uses of the study drug. The maximum daily dosage should be one bottle (100 mL).

Randomization (Allocation)

Participants will be randomly assigned to either the IP group or the PI group with a 1:1 allocation using the permutation random block method; they will be stratified by category according to whether a maxillary third molar is to be extracted in addition to a mandibular third molar. The block size will not be disclosed to ensure that blinding is maintained. The allocation sequence for the randomization method will be generated by the biostatistician. The trial participants, care providers, and outcome assessors will be blinded. Because this is a crossover study in which both groups receive the actual drug, an unblinding procedure will not be incorporated into the study.

All subjects providing consent to participate, fulfilling the inclusion criteria, and not meeting any of the exclusion criteria will be randomized. The principal investigator or subinvestigator will send a subject enrollment form by email to the data center. The staff at the data center will confirm the eligibility of the participants and issue them the enrollment confirmation form that contains the eligibility judgment, randomization assignment result from the generated random sequence, and enrollment

number. The form will then be sent to the principal investigator or subinvestigator.

Primary End Point and Secondary Efficacy and Safety End Points

The primary end point is the change in the within-subject VAS immediately before and 5 minutes after the use of the first ibuprofen or placebo gargle on PODs 1 and 2 (ΔVAS_5_ibuprofen − ΔVAS_5_placebo and ΔVAS_5_placebo − ΔVAS_5_ibuprofen).

The secondary efficacy end points are the following:

1. Δwithin-subject VAS before and 15 minutes after the first use of the ibuprofen or placebo gargle on PODs 1 and 2 (ΔVAS_{15}_ibuprofen – ΔVAS_{15}_placebo)

2. ΔVAS before, and 5 and 15 minutes after the use of the first ibuprofen gargle on PODs 3 through 5

3. Overall daily efficacy on PODs 1 through 5

4. Number of uses of the gargle and analgesic drug per day on PODs 1 through 7

As a strategy to improve adherence to the intervention protocols, the ibuprofen and placebo gargles will be prepared according to each POD (5 bottles, 1 for each POD from 1 to 5). The patients will return the bottles of gargle at the end of the treatment period; the amount of any remaining solution will be measured and recorded.

The secondary end point for safety is the presence or absence of adverse events associated with the conduct of this clinical study.

Time Schedule of Intervention, Outcomes, and Other Assessments

The relationships between the interventions, outcomes, other assessments, and visits associated with the participants of this study are shown in Table 1.

Table 1. Summary of study assessments and procedures.

Time point	Study period							
	Enrollment	Allocation	Postallocation					Close-out
	POD[a] 0 (pre-extraction)	POD 0 (postextraction)	POD 1	POD 2	POD 3	POD 4	POD 5	PODs 6 to 10
Enrollment								
Eligibility screen	✓							
Informed consent	✓							
Registration	✓							
Surgical information[b]	✓	(✓)[c]						
Allocation		✓						
Interventions								
I[d] then P[e]			✓					
P then I				✓				
I					✓	✓	✓	
Assessments								
VAS[f] (5 min)			✓	✓	(✓)	(✓)	(✓)	
VAS (15 min)			✓	✓	(✓)	(✓)	(✓)	
Diary[g]			✓	✓	✓	✓	✓	✓
Adverse events			✓	✓	✓	✓	✓	✓

[a]POD: postoperative day.

[b]Sex, age, reason for extraction, side of extraction, Pell-Gregory classification, Winter's classification.

[c]items collected on a voluntary basis and not mandatorily.

[d]I: ibuprofen.

[e]P: placebo.

[f]VAS: visual analog scale.

[g]Total amount of rescue medications, number of tablets, number of analgesics used (gargles), self-reported global efficacy.

Participant Retention

Following tooth extraction and suturing, an appointment will be scheduled for suture removal approximately 1 week after the procedure. We believe that scheduling the suture removal appointment immediately postoperatively will help patients comply with the protocol. Data from participants who discontinue their participation in the study or those who deviate from the protocol will be included in the full analysis set.

Data Collection and Management

The primary investigator or subinvestigator will enter the case report form (CRF) data for each participant into the electronic data capture system. The principal investigator will confirm that the entered CRF data are complete and correct, electronically sign the CRF in the electronic data capture system, and then obtain a printout of the signed CRF for filing. The CRF printout will be retained. If there are any queries about the CRF data that are entered by the staff at the data center, the primary investigator or subinvestigator should respond promptly to these queries. Only the biostatistician will have access to the final data set.

Statistics

Sample Size Calculation

The target number of subjects is 40, with 20 subjects in the IP group and 20 in the PI group. In a previous report involving healthy subjects and patients with chemotherapy- or chemoradiotherapy-associated oral mucositis [25], the mean ΔVAS and SD of pain relief after 3 days of use were −1.28 and 0.84 (n=7 patients), respectively, of which the preuse VAS value for the ibuprofen gargle was >3. In the subgroup with a VAS≥3 before ibuprofen gargle use, the ΔVAS was −1.56, and the ΔSD was 0.81 (n=5).

In this study, we estimate a ΔVAS_5 of −1.5 and ΔSD of 1.2 for ibuprofen gargles, and a ΔVAS_5 of −0.7 and ΔSD of 1.2 for placebo gargles, assuming a placebo effect of less than half the ΔVAS_5 of ibuprofen gargles. Therefore, for obtaining a mean within-subject difference of 0.8 in ΔVAS_5 (ΔVAS_5_ibuprofen − ΔVAS_5_placebo), a common ΔSD of 1.2, a ratio of 0.8-1.2 for between- and within-subject variance, an alpha error of .05, and a beta error of .1, a total of 30 cases are required. Hence, considering a potential withdrawal rate of 25%, we plan to enroll 40 patients (20 per group).

No additional analyses (eg, subgroup and adjusted analyses) will be performed.

Analysis

A summary of the planned statistical analysis for this study is provided below. The final analysis will be performed after data from the subjects are obtained and locked at the end of the follow-up period.

The full analysis set is the set of randomized subjects who receive at least 1 dose of the study drug and excludes those without baseline data or with major protocol violations (eg, absence of informed consent or enrollment outside the study period). The per protocol set is the subset of subjects in the full analysis set who comply sufficiently with the protocol and excludes those associated with any of the following: violation of the inclusion criteria, violation of the exclusion criteria, and missing primary end point data.

The safety analysis set is the set of subjects who receive at least 1 dose of the study drug.

Handling of the Data

If there is any doubt about the data summarization or analysis, the biostatistician and the study representative will discuss the issue and decide how it will be addressed. When missing data are identified, the researcher will contact the subject. If the within-subject difference or ΔVAS cannot be calculated owing to missing VAS values, the within-subject difference or ΔVAS at that time will be recorded as 0. If any missing or deficient values other than the VAS values are not obtained, no analysis will be performed.

Primary Analysis

In this study, the mean and SD of ΔVAS_5 on PODs 1 and 2 and, where appropriate, the 95% CI of the mean will be calculated. We will also calculate the mean and SD of the within-study difference in ΔVAS_5 and, where appropriate, the 95% CI of the mean. The treatment effect will be estimated by dividing the mean of ΔVAS_5 in the within-subject difference by 2 and calculating the *P* value using an unpaired *t* test.

Secondary Analysis

The mean and SD of ΔVAS_{15} on PODs 1 and 2 and, where appropriate, the 95% CI of the mean will be calculated. We will also calculate the mean and SD of the within-study difference in ΔVAS_{15} and, where appropriate, the 95% CI of the mean. The treatment effect will be estimated by dividing the mean of ΔVAS_{15} in the within-subject difference by 2 and calculating the *P* value using an unpaired *t* test.

The mean and 95% CIs of ΔVAS_5 and ΔVAS_{15} for PODs 3-5 will be calculated for each group. Analysis of covariance with the preuse VAS value or the strata factor as a covariate will be performed to calculate the adjusted ΔVAS_5 and ΔVAS_{15} and their 95% CIs for each group. We will calculate summary statistics for the overall daily efficacy on PODs 1-5, scale by scale and group by group. Summary statistics will be calculated for each group for the number of times ibuprofen or placebo-containing products and analgesics are used on PODs 1-7.

Adverse Events

We define an adverse event as any disease, disability, death, or infection that occurs during this study. Adverse event monitoring will begin on POD 1 and continue up to POD 5, inclusive. The principal investigator or subinvestigator will record all the adverse events in the CRF and treat and monitor the patient until resolution during the study. If the principal investigator or subinvestigator finds a potentially causal relationship between the adverse event and the study drug, all adverse events will be recorded for reporting to the review board. This study is insured for clinical trials, with up to approximately US $385,000 guaranteed for death cases.

Monitoring for Compliance With Human Rights and Welfare

Periodic monitoring of the study will be performed to confirm if the human rights and welfare of the subjects are being protected, the study is being conducted safely in accordance with the protocol and the applicable regulatory requirements

under the Clinical Trials Act, and the data are being collected properly. The principal investigator will appoint a responsible monitor and other monitors for the study. The items to be checked during monitoring are specified in the written procedure for monitoring the study. Any changes required by the ethics committee will be communicated to the participants by the investigators.

For quality assurance, the study will be examined to determine if it is being conducted in accordance with the protocol and written procedures, independently and separately from the routine monitoring activities.

Results

Participant recruitment began on June 1, 2021. The expected date of completion (last visit of the last patient) is September 30, 2022. All data acquired during the study period will be analyzed. Additionally, as this is a short-term trial performed over 7 days, an evaluation of the interim results is not planned.

This manuscript is based on the current version of the study protocol (version 1.1, last updated on March 1, 2021). The study was first authorized on March 1, 2021. The results of this study will be available on the Japan Registry of Clinical Trials website. The results will also be disseminated via presentations at regional and international conferences, such as those for dentistry and oral and maxillofacial surgery. The results will also be submitted for publication in a peer-reviewed journal.

Discussion

Significance of the Study

This single-center, placebo-controlled, double-blind, randomized crossover trial will be the first well-designed clinical study to evaluate the efficacy of an ibuprofen gargle for relieving postoperative pain after extraction of mandibular third molars. Postoperative pain management after third molar extraction is essential, and NSAIDs are the first-line treatment. To address the side effects of oral NSAIDs, this study will compare a topical ibuprofen gargle with a placebo. Previous studies have not compared the use of ibuprofen and a placebo. The anticipated findings in this study are that the topical ibuprofen gargle will be more effective than the placebo in controlling postoperative pain after third molar extraction.

Overview

Mandibular third molars are commonly extracted, and postoperative pain is a major complication resulting from the extraction. Symptomatic pharmacological treatment aims to provide postoperative pain relief. Continuous medication with NSAIDs is recommended as the first-line treatment after extraction of mandibular third molars to relieve pain and inflammation. Oral administration of NSAIDs can lead to various adverse effects; therefore, topical NSAIDs are preferred to minimize these side effects [9,27,28]. The problem with the administration of NSAIDs thrice a day is that the analgesic effect wears off and postextraction pain recurs. Several methods of treating intermittent pain with analgesic rinses have been reported in the past, but none have been approved in Japan [18,27,28]. Additionally, to date, there have been few well-designed clinical studies evaluating the efficacy and safety of analgesic gargles to relieve postoperative pain after mandibular third molar extraction. Thus, recent studies have focused on the development of topically administered NSAIDs in the form of gels, toothpastes, and rinses [27,28]. However, few studies have highlighted the benefit of ibuprofen gargles for postoperative pain after tooth extraction. We believe that an ibuprofen gargle can be used after third molar tooth extraction to provide seamless pain relief between doses of NSAIDs when additional pain relief is required before the next dose of NSAIDs is due.

Safety Concerns

Regarding the safety concerns associated with the ibuprofen gargle, the gargle is retained in the mouth for only approximately 1 minute before being discarded. Therefore, systemic absorption of ibuprofen is unlikely. Moreover, the concentration to be used in this study (600 mg ibuprofen/100 mL) is equal to the maximum daily allowance (600 mg) approved for oral ibuprofen, and if used according to the recommended method, the amount of drug that could be ingested accidentally is less than the maximum daily allowance. Therefore, adverse events due to orally absorbed ibuprofen are less severe than or identical to those reported for oral ibuprofen.

Rationale

For ethical reasons, only ibuprofen-containing gargles will be used from POD 3. The reason for the crossover study between POD 1 and POD 2 was that the median duration of the effect of the ibuprofen-containing gargle was approximately 20 minutes in our previous study, and there was no carryover effect when comparing POD 1 and POD 2 [25]. Therefore, we chose an ibuprofen gargle as the test drug for treating patients after mandibular third molar extraction and decided that a period of 5 days was sufficient for a short-term treatment study. Adverse events and all conditions that occur will be recorded and observed until the conditions subside within the study period, regardless of whether there is a causal relationship with the clinical study.

Strengths

Because previous clinical trials used only ibuprofen-containing drugs without a placebo or control group, this clinical trial is designed as a placebo-controlled comparative study to examine the placebo effect. Therefore, this study will compare an ibuprofen gargle with a placebo for treating postoperative pain after mandibular third molar extraction; it will be performed as a phase II, placebo-controlled, double-blind, randomized crossover trial.

Limitations

The main limitation of this study is the short duration (7 days).

Conclusions

Postoperative pain management after third molar extraction is essential, and NSAIDs are the first-line treatment. To address the side effects of oral NSAIDs, this study will compare a topical ibuprofen gargle with a placebo. The results of this study could provide valuable evidence to support the use of an ibuprofen

gargle for patients after mandibular third molar extraction. In addition to NSAIDs, ibuprofen gargles may relieve the pain caused by mandibular third molar extraction. This study fills a gap in the literature and may lead to a safer, but still effective, pain relief option to improve patients' postoperative comfort.

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Authors' Contributions

YK is the chief investigator, involved in the conception and design of the study, and drafting of the manuscript. TI obtained funding and designed the statistical analysis plan, managed the study, and reviewed the manuscript. T Ito managed the study and drafted the manuscript. YO, TH, IY, and MA reviewed the manuscript. All authors have approved the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CRF: case report form
IP: ibuprofen-placebo
jRCT: Japan Registry of Clinical Trials
NSAID: nonsteroidal anti-inflammatory drug
PI: placebo-ibuprofen
POD: postoperative day
VAS: visual analog scale

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Protocol

Effectiveness of Silver Diamine Fluoride for Preventing Occlusal Caries in the Primary Teeth of Preschool Children: Protocol for a Randomized Controlled Trial

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Abstract

Background: Tooth decay is a significant public health problem globally. The caries-arrest effectiveness of 38% silver diamine fluoride (SDF) has been well documented. However, information on the caries-preventive effect of SDF on primary teeth is insufficient.

Objective: The aim of this trial is to investigate the effectiveness of semiannual application of 38% SDF and that of 5% sodium fluoride (NaF) varnish when compared with placebo control for preventing occlusal caries in the primary molars of preschool children over 30 months.

Methods: This 3-arm, parallel design, double-blind, randomized controlled trial involves 791 preschool children. Children are randomly allocated to receive 1 of 3 interventions as follows: Group 1, 38% SDF; Group 2, 5% NaF varnish; and Group 3, placebo control (tonic water). The intervention and dental examination will be carried out every 6 months. A parent-administered questionnaire, including the children's demographic background and oral health–related behaviors, has been collected at baseline. Follow-up examinations to detect new caries development will be conducted every 6 months by a masked examiner. Caries development will be diagnosed at the cavitation level. Chi-square tests and logistic regression analyses will be adopted. A 2-level logistic regression analysis will be performed to investigate the effects of the study interventions and other potential confounding factors on the development of occlusal caries.

Results: This study was started on September 1, 2020, and the recruitment process ended on September 30, 2021. At present, a total of 791 children are participating in the study. This 30-month clinical trial is expected to be completed in March 2024.

Conclusions: If SDF application is more effective than NaF varnish for preventing caries on occlusal surfaces of primary teeth, it can be a preferred choice for caries prevention in a kindergarten-based program. Results of this trial will provide valuable clinical evidence for the development of oral health strategies and policies on the promotion of child oral health.

Trial Registration: HKU Clinical Registry HKUCTR-2844, https://tinyurl.com/bdhz9yuk; ClinicalTrials.gov NCT05084001, https://clinicaltrials.gov/ct2/show/NCT05084001

International Registered Report Identifier (IRRID): DERR1-10.2196/35145

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KEYWORDS

silver diamine fluoride; sodium fluoride; children; early childhood caries; prevention

Introduction

Background

Tooth decay or dental caries is a silent epidemic. According to the Global Burden of Disease Study, dental caries in primary teeth remains a public health problem affecting more than 530 million children globally [1]. The term "early childhood caries" (ECC) has been used to describe the presence of one or more decayed, restored, or missing primary teeth in a child younger than 6 years [2]. In Hong Kong, more than half (55%) of 5-year-old children have untreated ECC, and the majority (>90%) of the decayed teeth are left untreated [3]. Children with untreated ECC may experience toothache, oral pain, and infection, leading to poor quality of life [4]. This also affects their family members' quality of life and eventually impacts the community. Severe consequences of ECC include emergency room visits and hospitalizations with high costs of treatment, and missing school, as well as negative impacts on the ability to learn [2]. In extreme cases, untreated ECC can lead to life-threatening conditions and even death [5].

An epidemiological study found that most (78%) cases of ECC in preschool children in Mainland China involved the primary molars [6]. In Hong Kong, decayed primary molars constituted more than half (56%) of all decayed primary teeth in preschool children [7]. High prevalence of premature loss of primary molars due to untreated tooth decay has been reported [8]. Tooth decay is commonly found on the occlusal tooth surface owing to the complex anatomy of the fissure system, which makes the surface difficult to clean, thereby promoting the accumulation of a bacterial biofilm and increasing the risk of developing carious lesions [6]. In addition, young children are not able to brush their posterior teeth properly, and they may not have supervised toothbrushing during the preschool period. Hong Kong preschool children's oral health has not improved over the last 2 decades [9]. An epidemiological dental survey in Hong Kong found that the prevalence of caries was much higher in older preschool children (38% at age 3 years and 55% at age 5 years) [3]. Currently, there is no government-subsidized dental care service for preschool children in Hong Kong.

Several strategies, including placement of dental sealant and topical application of sodium fluoride (NaF) varnish, have been proposed to prevent occlusal surface caries. Nevertheless, it is a challenge to place dental sealants in the primary molars of young children because the application is technique sensitive and requires optimum tooth isolation. NaF varnish is another potential agent for preventing dental caries, but it is not cost-effective in the context of government-funded services [10]. The relatively high cost of professionally administered fluoride varnish has hindered its widespread adoption in many countries [11]. Recently, silver diamine fluoride (SDF) has been considered a therapeutic agent for treating cavitated dental caries lesions in young children and those with special needs [12]. Several laboratory studies have documented its antibacterial effects in inhibiting cariogenic bacteria and its remineralizing effects [13]. Results of randomized clinical trials have shown its caries-arresting effects in preschool children [14-16]. No major adverse effects of SDF were observed, except dark staining on treated lesions after application [17]. A systematic review concluded that the caries arrest rate of 38% SDF was as high as 81% (95% CI 68%-89%; $P<.001$) [18]. In light of this, the American Academy of Pediatric Dentistry developed a guideline on the use of 38% SDF for arresting cavitated dentin caries lesions in primary teeth among children [12]. Recently, another systematic review and network meta-analysis concluded that semiannual application of 38% SDF solution showed the highest effectiveness for caries arrest in advanced cavitated lesions on coronal surfaces [19].

Nevertheless, clinical evidence for the dental caries–preventive effect of SDF is scarce [20]. Therefore, to fill this knowledge gap and to provide the needed clinical evidence to guide dental practice and public dental care service, this study aims to investigate the preventive effect of SDF versus NaF varnish and a placebo control on the occlusal surfaces of the primary molars of preschool children. In addition, this study will evaluate parental satisfaction with their child's dental status and dental appearance, and the adverse effects of SDF application.

Objectives

The objective of this study is to compare the effectiveness of 38% SDF, 5% NaF varnish, and a placebo control for preventing dentine caries in the primary molars of preschool children when applied semiannually over 30 months.

Hypothesis

The null hypothesis tested is that there is no difference in the effectiveness of 38% SDF, 5% NaF varnish, and a placebo control for preventing dentine caries of the occlusal surfaces of the primary molars in preschool children when applied semiannually over 30 months.

Methods

Ethics Considerations

Ethics approval has been obtained from the Institutional Review Board of The University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HAHKWIRB; IRB reference number: UW20-028).

Trial Design

This is a 3-arm, parallel-design, double-blind, randomized controlled trial consisting of semiannual application of SDF, semiannual application of NaF varnish, and a placebo control. Similar school-based oral health education will be provided to the children and parents in all participating kindergartens. This study will be reported following the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (Multimedia Appendix 1). Before subject recruitment, the study was registered on January 17, 2020, at HKU Clinical Registry, which is a publicly accessible database, with the reference number HKUCTR-2844. Later, it was registered as a clinical trial by the United States National Library of Medicine (ClinicalTrials.gov) on October 19, 2021, with the registration number NCT05084001, as an additional registration.

Patient and Public Involvement

Kindergartens that have participated in the school oral health program provided by the Faculty of Dentistry, The University of Hong Kong were invited. Research assistants will assist in all stages of the trial, mainly as contact persons and as persons in charge of inviting kindergartens, explaining the whole trial to kindergartens, and clarifying their queries. After the principals agreed to take part in this study, an information sheet containing the aim of the study and the details of the research study and procedures was distributed to parents or guardians of the children. Parental consent in written form was obtained before conducting this trial. The participant children and their parents are at liberty to withdraw from this study at any time. They are also free to seek further dental treatment with their own means and preferences.

Eligibility Criteria

The eligibility criteria for participants are as follows: (1) age 3-4 years, (2) healthy status, (3) presence of at least one caries-free (no cavitation) primary molar, and (4) parental written consent. The exclusion criteria are as follows: (1) no cooperation or refusal to undergo examination, (2) major systemic illnesses, (3) presence of acute pain, infections, gingival ulceration, or stomatitis, (4) known sensitivity to silver or other heavy-metal ions, and (5) current involvement in any other research that may impact this study. At the tooth level, primary molars with developmental defects; presence of dental sealants or fillings; presence of pain, fistulas, abscesses, mobility, or discoloration; or any sign of nonvitality are excluded.

Recruitment and Examination

All phases of this trial will be carried out in the kindergarten that the children attend. The research team includes dentists and research assistants. Before conducting the trial, the whole team was trained by experienced specialists in dental public health. A calibrated and trained examiner screened the children who had written parental consent. All children were clinically examined, and those who met the inclusion criteria were selected. No dental radiograph examination was conducted. If a child has more than one caries-free primary molar, all of the molars will be included. At baseline and the semiannual follow-up examinations, clinical examination of the children will be conducted by a trained dentist who will be masked to the group assignment of the participant children. All clinical investigations will be conducted in kindergartens. The study children will lie on a bench and will be examined in the supine position. Tooth status will be assessed by careful visual inspection with a dental mirror attached to a handle with a light-emitting diode for intraoral illumination (MirrorLite, Kudos Crown Limited). A microbrush will be used to remove food debris and dental plaque that obstruct inspection. A World Health Organization CPI probe with a 0.5-mm ball tip will be used to confirm the presence of a carious cavity when necessary. Great care will be taken to avoid damaging the tooth surface during probing. The intervention will be free, and participants or kindergartens will not pay any cost for the research. After the examination, parents will receive a brief report on their children's dental caries status.

Caries will be diagnosed at the cavitation level following the criteria recommended by the World Health Organization. Drying of the tooth surface with air blow will not be carried out in this study. An occlusal tooth surface will be recorded in one of the following categories: (1) sound, (2) caries confined to the enamel or into dentin but without cavitation, (3) cavitated dentin caries (active), (4) cavitated dentin caries (arrested), (5) filled surface, (6) extracted tooth, and (7) tooth with nonvital signs, such as abscess or fistula. The decayed, missing, and filled tooth surface (dmfs) index will be adopted for documenting dental caries experience. Oral hygiene status will be measured using the visible plaque index (VPI). The buccal and lingual surfaces of 6 index teeth (Fédération Dentaire Internationale tooth numbers 55, 51, 63, 71, 75, and 83) will be thoroughly examined. The presence or absence of visible plaque on the occlusal surface will be recorded. Black staining on each surface will be clinically observed and recorded (yes/no). A random sample of 10% of the study children will be re-examined on the same day at the baseline and follow-up examinations to evaluate intraexaminer reproducibility. The study follow-up is every 6 months. If some parents of the study children seek early professional intervention, all the sealed, restored, or extracted teeth will be recorded as study treatment failure.

Questionnaire Survey

A parental questionnaire consisting of 3 fields (child's information, child's oral health–related behavior, and family information) will be administered at baseline and at the 30-month follow-up visit. It will collect information regarding the child's oral hygiene practice, use of fluoride agents, dental visit behavior, snacking habits, parental educational level, and family income. The questionnaire will also assess parental satisfaction with their child's oral health and dental esthetics. In the follow-up questionnaire, parents will be asked to report posttreatment complications of the assigned treatment, such as pain from the treated teeth and gingival irritation around the treated teeth.

Random Allocation, Concealment, and Blinding

With regard to treatment group allocation and intervention, at baseline, participant children were stratified into the following 2 groups: (1) with dmfs score 0 and (2) with dmfs score >0. The children were allocated by a stratified randomization method with varying random block sizes, using a personal computer, into 1 of 3 intervention groups. The unit of treatment allocation was at the subject level. The allocation sequence was generated by a technician who was not involved in the examination and random allocation.

Regarding allocation concealment, a randomization scheme was produced, and a random code for each participant was placed in an opaque envelope. The dental team did not know the treatment allocation before the time of applying the material. The envelope was opened by a dental assistant, and then, the materials were prepared following the assigned intervention of the child according to group allocation. The children and their parents have not been informed about their group allocation. The examiner will also be blinded to the assigned intervention. However, the dentists who will provide the interventions will

not be blinded because the agents (SDF, NaF, and placebo) look dissimilar in nature.

Interventions

Occlusal molar surfaces without cavitated dentine caries lesions were randomly allocated to receive SDF, NaF varnish, or a placebo control. Clinical examinations will be conducted every 6 months after the intervention.

The treatment interventions are as follows: (1) Group A, semiannual topical application of 38% SDF solution (Saforide, Toyo Seiyaku Kasei Co, Ltd); (2) Group B, semiannual topical application of 5% NaF varnish (Duraphat, Colgate Palmolive); (3) Group C, semiannual topical application of a placebo control (tonic water).

The application procedure is as follows:

1. Remove food debris and dental plaque, if any, from the occlusal surface to allow good contact between the study agent and tooth surface.
2. Isolate the occlusal surface of sound primary molars with cotton roll or gauze. For Group A, dispense 1 drop (0.05 mL) of 38% SDF solution, which contains approximately 2.2 mg fluoride ions, in a plastic dappen dish. For Group B, dispense 1 drop (0.25 mL) of 5% NaF varnish, which contains approximately 5.6 mg fluoride ions, in a plastic dappen dish. For Group C, dispense one drop (approximately 0.05 mL) of tonic water in a plastic dappen dish.
3. Slightly bend a microapplicator, and dip it in the agent.
4. Apply the agent with the microapplicator directly onto the occlusal surface of sound primary molars in each quadrant. One application is used for 1 quadrant (1 or 2 primary molars). If a child has 8 sound molars, he or she will receive a maximum of 4 applications on that day.
5. Gently rub the occlusal surfaces with the microapplicator while continuing to isolate the treated teeth whenever possible and ensure that the entire occlusal surfaces are wetted by the agent.
6. Minimize contact of the SDF solution with adjacent gingiva or mucosa to avoid potential soft-tissue irritation.

Subsequently, the study children will be instructed not to eat and drink for 30 minutes after application. The intervention will be provided every 6 months. Application of the appropriate agent (either 38% SDF, 5% NaF, or tonic water) will be carried out after an oral examination according to the assigned treatment group. The schedule of subject enrollment, interventions, and outcome assessments is shown in Figure 1.

Parents of all study children will be invited to attend an oral health talk by a dentist once a year. A presentation aided by color photographs and slides about child oral care will be given to parents in the kindergartens. A set of a toothbrush and fluoridated toothpaste will be given to all study children as a souvenir once a year. After the examination, a report on the child's oral health status, including caries status, and leaflets about the child's oral health will be sent to the parents.

Figure 1. Schedule of subject enrollment, interventions, and outcome assessments. NaF: sodium fluoride; SDF: silver diamine fluoride.

		Study period						
		Enrollment	Allocation	Postallocation				
Timpoint		$-t_1$	0 mo	6 mo	12 mo	18 mo	24 mo	30 mo
Enrollment								
	Eligibility screen	✓						
	Informed consent	✓						
	Allocation		✓					
Interventions								
	Group A: 38% SDF		←	—	—	—	—	→
	Group B: 5% NaF		←	—	—	—	—	→
	Group C: placebo		←	—	—	—	—	→
Assessments								
	Caries status	✓	✓	✓	✓	✓	✓	✓
	New caries			✓	✓	✓	✓	✓

Outcome Measure

Information related to the outcomes of the trial will be collected at baseline and thereafter semiannually for 30 months.

Primary Outcome

The treatment will be classified as "success" if an occlusal surface at baseline does not develop cavitated dentin caries

lesions at the follow-up examination. "Failure" will be recorded if the surface develops cavitated dentin caries; the tooth has received dental sealant placement, a crown, or occlusal fillings; or the tooth is missing due to caries.

Secondary Outcomes

Parent's satisfaction with their child's dental health and dental appearance will be measured using a 5-point Likert scale, ranging from 1 (very dissatisfied) to 5 (very satisfied).

Information on the adverse effects of SDF treatment, such as tooth pain, gingival irritation, and systemic toxicity (eg, nausea and vomiting), will be collected through a parental questionnaire within a week after the intervention. During the follow-up examination, the examiner will look for signs and symptoms of potential side effects, including blackening of the treated teeth and adjacent teeth. Regarding parental satisfaction, questionnaires will be distributed to assess parent's satisfaction with their child's oral health and dental appearance before the trial and at the 30-month follow-up.

Sample Size Calculation

Based on previous studies [3,21], the anticipated proportion of sound occlusal surfaces at baseline developing into cavitated dentin lesions at the 30-month follow-up is approximately 25%. An absolute difference of 10% in the rate of new caries development (proportion of occlusal surfaces that develop cavitated dentin lesions at 30 months) between 2 intervention groups is considered to be clinically significant. The estimated sample size is based on the expected proportion of the development of new cavitated occlusal caries in primary molars, with the power of the study set at 90% (β=.1) and with a 2-sided test at the 5% statistical significance level. The sample size per study group, calculated by using the G*Power 3.1.9.2 software (University of Düsseldorf, Germany) is 351 sound occlusal tooth surfaces. The estimated intraclass correlation coefficient (ICC) for dental caries data at the surface level within the individual is approximately 0.5 [22]. Based on our previous survey [3], we anticipated that the mean number of sound occlusal surfaces per child would be 6 at baseline. Following the equation for the required sample size in a multilevel model, the design effect will be 3.5. Thus, the estimated sample size would be at least 1229 sound occlusal surfaces and with at least 205 children in each study group or 615 in total at baseline. The anticipated dropout rate after 30 months is 20%. Thus, 769 children in total need to be recruited at baseline. The estimated participation rate is approximately 90%, and therefore, at least 854 children have to be invited to join the study.

Data Analysis

The collected data will be entered into a Microsoft Excel file by 2 persons, and the data will be proofread to minimize data entry error. Data will be analyzed using the SPSS software for Microsoft Windows (SPSS Inc). Intraexaminer agreement in caries diagnosis will be assessed by using Cohen kappa statistics. Since more than one molar may be selected from 1 child, multilevel data analysis will be carried out.

A chi-square test and *t* test will be performed, when appropriate, to assess the differences between groups with regard to their baseline demographic background, oral health–related behaviors, and caries experience. A chi-square test will be used to evaluate the differences in new caries development and parental satisfaction among groups. Thus, 2-level generalized estimating equation models with a logit link function (child level and surface level) will be adopted to evaluate the variables influencing the occurrence of occlusal caries at the 30-month follow-up. Independent variables include the child's background characteristics (gender, place of birth, father's and mother's education levels, and family income); the child's clinical characteristics at baseline (tooth type, such as upper or lower molars and first or second molars, presence of plaque on the occlusal surface, caries experience, and overall oral hygiene); and the child's oral health–related behaviors (use of fluoride agents, dental visit behavior, and snacking habit). The backward elimination method will be adopted for modeling. A McNemar test will be performed to compare the differences in parent's satisfaction with their child's dental appearance and dental health at baseline and the 30-month follow-up. The level of statistical significance for all tests will be set at .05. An intention-to-treat (ITT) analysis will be adopted so that all study children who are randomized and all events will be accounted for in the primary analysis. The relevant government agencies have access to the collected data for the purposes of verifying the integrity of the study data and evaluating compliance with the study protocol. Regarding confidentiality, hard copies of the data will be stored in a sealed box in a locked room during the trial and after publication for 5 years. In addition, the research findings will be presented in scientific conferences for clinicians and health care researchers, and will be disseminated to the community and stakeholders through oral health educational seminars and talks.

Results

This study was started on September 1, 2020, and the recruitment process ended on September 30, 2021. At present, a total of 791 children are participating in the study. This 30-month clinical trial is expected to be completed in March 2024.

Discussion

This is a randomized, 3-arm, double-blind, parallel-design clinical trial that aims to investigate the effectiveness of semiannual application of 38% SDF, 5% NaF varnish, and placebo for preventing new caries on occlusal surfaces of primary molars. We hypothesize that SDF has a better effect for preventing occlusal caries than NaF varnish and control owing to its promising results in remineralizing initial enamel caries lesions [23]. The caries-arresting effects of SDF in preschool children have been well documented. However, there is limited information on the effectiveness of SDF for primary prevention purposes in young children. The effect of SDF on caries in primary teeth was systematically reviewed [20,24]. Unfortunately, all included studies in the meta-analysis primarily focused on therapeutic effect, and SDF was applied to decayed teeth. So far, there is insufficient evidence regarding the preventive effect of SDF in primary teeth in vivo. Therefore, it

is essential to investigate the caries-preventive effects of SDF versus NaF varnish and placebo control on the occlusal surfaces of the primary molars of preschool children. It should be noted that the children in the placebo group will not receive substandard care, since there are no existing government subsidized programs that provide professionally applied topical fluorides to prevent dental caries in kindergarten children. In fact, all participant children will have additional benefits from regular dental check-ups and receive a free toothpaste and toothbrush. Parents of the study children will receive oral health information through distributed leaflets and oral health seminars in the kindergarten.

Preventing the development of ECC is the ultimate goal of a disease management plan. Based on recent epidemiological studies, ECC remains prevalent globally [25], and the situation is more challenging in low-income countries [26]. An innovative evidence-based preventive program is needed. Since the proposed caries prevention protocol is feasible, affordable, and noninvasive, if shown to be effective, it can be adopted in a school-based or community-based setting to prevent ECC in children from disadvantaged communities. The strength of this study is adequate sample size, thus leading to sufficient study power. A limitation of this study is that the results of this trial conducted in healthy young children may not be translatable to other groups of children who have special health care needs or other age groups. A further study on the preventive effect of SDF conducted in patients with special health care needs is required. We plan to disseminate the research findings to different audiences as follows: (1) For dental practitioners and dental educators, the research findings will be published in international peer-reviewed journals and presented at scientific conferences; (2) For community health care teams, kindergarten teachers, and stakeholders, workshops about caries prevention for preschool children will be arranged in Hong Kong; and (3) For end users (children and parents), a story and brief summary of the research findings will be presented in plain language through newsletters and videos on the faculty website, as well as local multimedia.

The results of this study will provide evidence to strengthen or refute the recommendation regarding the use of SDF for preventing occlusal caries in primary molars. The study findings can guide decision-making among dental practitioners and health policymakers regarding whether SDF should be included in a school-based caries prevention program.

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Authors' Contributions

DD contributed to the conception and design, acquisition of data, or analysis and interpretation of data; planned the research timeline; and drafted and critically revised the manuscript. SH contributed to the conception and design, acquisition of data, or analysis and interpretation of data; performed the baseline examination; and critically revised the manuscript. SSG and CHC contributed to the conception and design, acquisition of data, or analysis and interpretation of data; provided training; supervised the fieldworkers; and critically revised the manuscript. ECML contributed to the conception and design, acquisition of data, or analysis and interpretation of data; supervised fieldwork project coordination; and critically revised the manuscript. All authors read, revised, and approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 182 KB - resprot_v11i5e35145_app1.pdf]

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Abbreviations

dmfs: decayed, missing, and filled tooth surface
ECC: early childhood caries
NaF: sodium fluoride
SDF: silver diamine fluoride

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Protocol

Dyadic Intervention for Sexually Transmitted Infection Prevention in Urban Adolescents and Young Adults (The SEXPERIENCE Study): Protocol for a Randomized Controlled Trial

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Abstract

Background: Adolescents and young adults (AYA) aged younger than 25 years have the highest rates of sexually transmitted infections (STIs) in the United States. Current STI prevention strategies for AYA rely primarily on individual approaches, leaving sexual partners with significant unmet sexual and reproductive health care and health education needs. Dyadic interventions may hold promise for harnessing the power of communal coping within relationship dynamics to enhance sexual decision making, communication, and behavior changes that reduce the future risk of STIs.

Objective: This paper describes the protocol and research methods of a dyad-based behavioral intervention that augments individual evidence-based interventions with joint health education counseling for heterosexual AYA dyads within a primary care setting. The trial aims to improve partner communication and collaborative sexual decision making and promote the adoption of sexual behaviors such as consistent condom use. The primary objective of this study is to assess the feasibility, acceptability, and effectiveness of a dyadic intervention targeted at preventing STIs in heterosexual couples in an urban setting.

Methods: A total of 100 AYA (50 dyads) aged 16 to 25 years, engaged in heterosexual intercourse, who reside in the city and are willing to recruit their main sexual partner for the study will be recruited and randomized into 2 groups, an intervention arm and a control arm. Participants will be recruited from an AYA medicine clinic and by using social media (Facebook and Instagram). The index participant and partner will complete a single individual session separately (Sister to Sister or Focus on the Future) with a gender-matched health educator. Dyads will then be randomized to receive an additional joint debriefing session together to discuss relationship dynamics, condom negotiation, etc. Participants will separately complete a telephone interview 6 weeks postintervention to determine the feasibility, acceptability, and impact of the intervention on mutual sexual negotiation, consistency of condom use, and communal coping skills, etc.

Results: So far, 25.4% (44/173) of eligible participants have been enrolled and randomized. Participants are mostly female (20/22, 91%), with at least a high school diploma (19/22, 86%), and 9 average lifetime sexual partners. Acceptability is high, with 98% (43/44) of participants expressing satisfaction with their study experience; 100% of dyads recruited were still together at 6-week follow-up.

Conclusions: Findings from this study will add to the current literature on the approaches to STI prevention, and its success will inform its application in risk reduction counseling for youth who are most at risk.

Trial Registration: Clinical Trials.gov NCT03275168; https://www.clinicaltrials.gov/ct2/history/NCT03275168

International Registered Report Identifier (IRRID): DERR1-10.2196/29389

(JMIR Res Protoc 2022;11(5):e29389) doi:10.2196/29389

KEYWORDS

STI; adolescent; young adult; youth; dyadic; sexual risk; heterosexual; health education; sexually transmitted disease; disease; adolescent; education

Introduction

Sexually transmitted infections (STI) have been on the rise in the United States, growing to epidemic proportions among adolescents and young adults (AYA) aged 15 to 24 years [1]. As a group, AYA account for the highest rates of STI, contributing more than 50% to the $16 billion in lifetime cost of the infection [2,3]. In addition to the heightened risk of STIs, AYA residing in low-income, densely populated urban communities experience racial and ethnic disparities and often have limited access to STI screening, treatment, and other sexual and reproductive health needs [4,5]. AYA have also been characterized as a vulnerable population due to cognitive factors such as inaccurate risk perceptions, increased biologic susceptibility (eg, cervical ectopy), engagement in unprotected intercourse, and sexual partnership patterns such as serial monogamy and concurrency [6-9]. National surveillance of the high school youth in the United States show that more than half of high school students are sexually active [9], and without access to services, they may suffer STI-associated sequelae. Despite the emerging public health threats and incidence of STIs in this age group, many AYA are not tested for STIs [10]. While the Centers for Disease Control and Prevention (CDC) guidance on the approach to STI prevention in youth is clear about the need for developmentally appropriate approaches to care, youth continue to face barriers to accessing sexual and reproductive health clinical services and education.

STI prevention efforts have primarily relied on individual approaches and heavily target girls and young women in heterosexual relationships, leaving young men with significant unmet sexual and reproductive health needs [11-13]. Young women are also diagnosed and treated for STIs more often compared to young men, who are often asymptomatic. As such, partner notification and treatment is a key strategy for disease control. Individuals with bacterial STIs often notify and refer their partners for treatment, but the relationship context influences the timing, manner of communication, and outcome of notification. Even so, less than half of male partners in a heterosexual relationship notified for STI treatment are successfully treated [12]. In response to this public health failure, many states are establishing regulations to implement expedited partner therapy [14-16]. In addition, the US Preventive Task Force recently recommended the integration of behavioral counseling as part of STI management, especially for adolescents at higher risk for new or recurrent disease [17]. This clinical change is estimated to have a moderate benefit and will reduce the probability of acquiring new STIs. The context for STI treatment services has also shifted from public health departments to primary care settings. Unfortunately, national data suggest that less than half of eligible patients are screened for STIs and many primary care providers serving youth fail to provide needed services [10,11,18]. Given the personal and societal costs associated with STIs, new models of care that integrate effective public health interventions into primary care settings are warranted. Public health departments have effectively used individual health educator models for STI/HIV risk reduction counseling but with limited effectiveness due to limited partner engagement. Efforts for engaging sexual partners of AYA using an integrated approach that combines behavioral interventions and health education and other methods are needed as individual level approaches fail to harness the power of joint intervention to improve sexual decision making and behavior.

Sexual relationships among AYA have long been believed to be delicate, short-lived, and lacking in commitment and mutual trust as compared to adult sexual partnerships. Evidence to the contrary proves that although youth, particularly males, tend to engage in extra-dyadic sex (sex with someone other than their partners) [6] and have higher tendencies toward concurrency and serial monogamy [19], STI in AYA is more nuanced and complex, often occurring in the context of committed relationships with or without concurrency. AYA relationships possess levels of trust and engagement, qualities that are relevant for and amenable to modifications for improving communication and promoting emotional and sexual satisfaction and negotiation skills. Such interventions can culminate in better self-management and a reduced risk of acquiring or transmitting STIs. Among adults, engagement of couples (or sexual dyads) for STI/HIV prevention have proven effective [20,21]. Research with AYA suggests that understanding early relationships may help prevent STIs but that we have failed to use our knowledge about the structure and function of romantic relationships occurring during this critical developmental learning period to engage youth for individual and dyadic behavior change. Formation of romantic relationships is a key task of adolescence with significant implications for young adult adjustment and health outcomes [22-24]. Male partners can be engaged through partnerships with female sexual partners [13]. Adolescent sexual dyads are formative and sufficiently stable for dyadic intervention, with relationships lasting 8 months on average [22]. Recent research with adolescent dyads also demonstrates that male and female partners report shared decision making and strong feelings toward their partners [24,25]. A dyadic approach to STI prevention allows both parties to see mutual responsibility for protecting each other from STIs, facilitates them working together, highlights the context and connection to disease acquisition, and provides a safe space for communication about difficult issues such as concurrency, while giving room for the dyad to learn key communication skills and receive support and guidance from a health professional. Although several studies demonstrate the effectiveness of adult-focused couple interventions for STI/HIV prevention, no

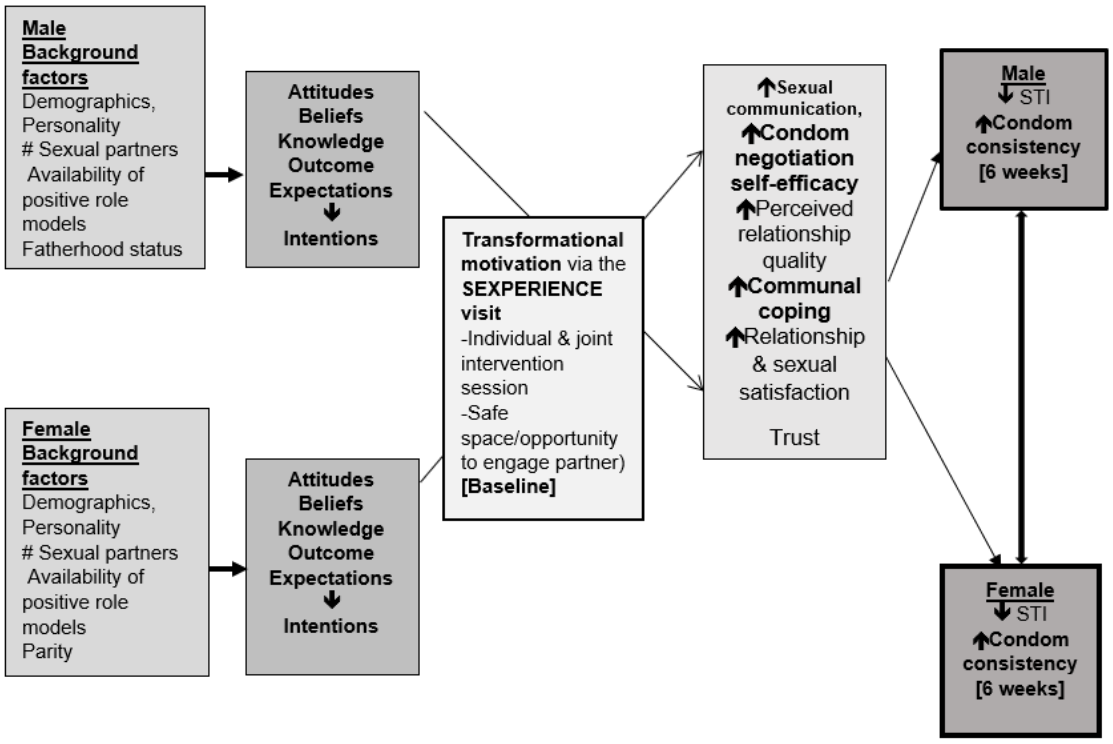
published studies address the AYA dyad as the unit of transformational change or have contextualized the interpersonal dynamics influencing individual sexual health behavior change within young romantic partnerships. To address this issue, the Sexperience study was developed using the tenets of transformational motivation theory to bolster the integrative model of behavior change as a conceptual framework [26,27]. The aim of this study is to examine the feasibility, acceptability, and effectiveness of a partner intervention in a community facing significant STI/HIV health disparities.

Methods

Study Design

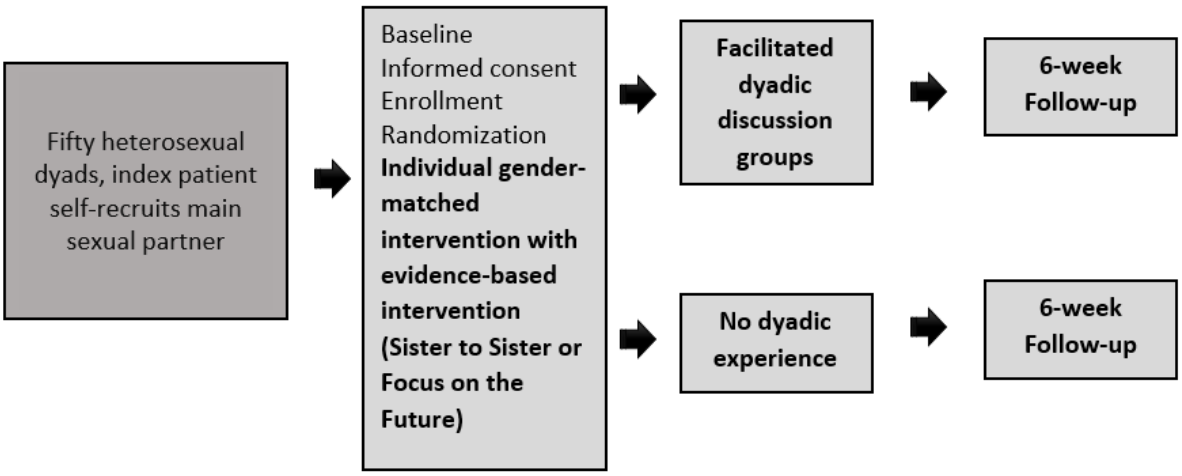
The Sexperience study is an exploratory randomized controlled trial designed to examine the feasibility, acceptability, and differences in short-term behavioral outcomes between youth who receive both individualized counseling and joint debrief with sexual partner and those who receive sexual risk reduction counseling alone. The study question operationalizes the tenets of transformational motivation theory [27] as a part of the conceptual framework (Figure 1) based on the integrative model of behavior which asserts that being in a relationship can change the member's behavior from one of self-centeredness to one that is driven to improve the relationship and is health enhancing. The integrative model of behavior serves as a backdrop for integrating the transformational motivation theory for dyadic research with AYA as a strategy to reach both female and male patients for treatment and preventive services [26]. The experience gained and lessons learned from previous research are invaluable tools for achieving the desired goals of this study [28].

Figure 1. Conceptual framework of the Sexperience intervention.



A total of 50 AYA dyads aged 16 to 25 years, engaged in heterosexual intercourse, who reside in the greater Baltimore (Maryland) metropolitan area (BMA) and are willing to recruit their main sexual partner for the study will be recruited and randomized. Participants are being recruited from an academic adolescent/young adult medicine practice and the BMA using social media (Facebook and Instagram). The index participant and their recruited partner complete an individual behavioral intervention session separately (Sister to Sister or Focus on the Future) with a gender-matched health educator. Dyads are then randomized to completion or to receive an additional dyadic debriefing session. Participants separately complete an exit survey at the end of the intervention and a telephone interview 6 weeks postintervention to determine the feasibility, acceptability and perceived impact of the intervention on mutual sexual and condom negotiation, consistency of condom use, and communal coping skills (Figure 2).

Figure 2. Overview of Sexperience study design.



Inclusion Criteria

Index participants are eligible if they are aged 16 to 25 years, live in the BMA, agree to recruit their main partner to the study, engage in male-female (heterosexual) intercourse, are willing to participate in a single individualized session with a health educator followed by a joint intervention, are willing to be contacted in 6 weeks for a telephone interview, have no reports of intimate partner violence with their current sexual partner, and have a current sexual partner within 5 years of their age. The partner must be aged 16 to 30 years based on adhering to prespecified age differentials to coincide with state law and developmental expectations, engage in male-female (heterosexual) intercourse, permanently reside in the BMA, and be willing to participate in a single individual session with health educator with or without a dyadic debriefing session with their partner and both health educators depending on randomization.

Exclusion Criteria

Index participants and partners who are unable to communicate with staff or participate in study procedures due to cognitive, mental, or language difficulties will not be eligible for recruitment into the study. Dyads will also be excluded if in same-sex main partnership or a member of the dyad is currently enrolled in another sexual behavior study, the patient/partner is currently pregnant, one or both partners has a known concurrent HIV infection, one or more partners has a pending incarceration, if there is more than 5 years age difference between the two partners, or there is evidence of intimate partner violence in the relationship.

Setting

Baltimore, Maryland, is the primary site of this study. Baltimore is a large city whose citizens face significant STI and HIV disparities. Baltimore was ranked the city with the highest STI rates by the CDC in 2020 [29]. The Maryland Department of Health and Mental Hygiene has determined that every county is a chlamydia hot spot, and county maps demonstrate that among hot spots, the city of Baltimore is the most densely affected. Although there are extremely low rates of youth noninsurance, the use of primary care providers for routine health maintenance drops off considerably. The Adolescent and Young Adult Clinic at Johns Hopkins established a Title X reproductive health clinic to serve the youth of Baltimore to aid in resolving the reproductive health access issues facing urban youth. The clinic sees over 200 unduplicated positive STI cases and partner referrals annually. Patients may also be referred for treatment through the Johns Hopkins Wellness Center, the Johns Hopkins Pediatrics Emergency Department, or the Baltimore City Health Department clinical sites.

Recruitment, Informed Consent, and Randomization

Recruiters will be available via phone during office and some evening hours in the clinic. Patients will be referred for study contact by their providers. Patients who agree to be contacted will be approached by a recruiter in person or via phone and if eligible, the dyad will be scheduled for written informed consent and intervention procedures. After enrollment, participants will be assigned to the control group or intervention group using a computer-generated randomization assignment. Envelopes based on dyadic study group number will be available to the research staff at the time of enrollment to adhere to the randomization sequence.

Sexperience Intervention

Following contact of prospective participants via social media or through the AYA practice by a member of the research team or the research coordinator, willing participants who agree to invite their sexual partners will be enrolled into the study when they bring their partners along to the clinic on a specified date

(usually within 2 weeks of agreeing to be in the study). Researchers will provide information to participants regarding the study and its processes individually and then seek informed consent. All participants who sign the informed consent with their partners will be randomized to either the intervention arm or control arm. Integral to the Sexperience intervention is the use of effective behavioral interventions designed to reduce STI/HIV risk behaviors, Focus on the Future and Sister-to-Sister, which will be used for male and female participants, respectively.

The Focus on the Future intervention [30] is an individual-level single session intervention designed to reduce the spread of heterosexually transmitted STI and HIV in African American males. This is achieved through education on correct and consistent condom use and motivation for sexual behavioral change. Sister to Sister [31] is a similar intervention designed for heterosexual females and aims to reduce the risk of HIV and other STI acquisition in AYA women. Sister to Sister, like Focus on the Future, is a 1-time brief intervention that encompasses training for skills building in sexual negotiation, demonstrations on the right way to insert a condom, and role playing. Both of these interventions have been shown to be effective in reducing STI risk and improving healthy sexual behavior.

The novel component of this intervention is that sexual partners will come together at the end of the individual sessions for a joint debriefing session that includes viewing of the condom negotiation videos and role-playing communication for condom use. At the end of the session with the Sexperience health educators, the patient will be able to state/demonstrate (1) understanding of the definition of STIs, (2) how to prevent future STI episodes, (3) proper use of male and female condoms, and (4) use of effective communication and condom negotiation strategies with their partner. Low-resource patients have been receptive to health educator support, and our preliminary studies indicate that improved communication between an adolescent and her partner occurs with the support of a professional who can educate and motivate adolescents with an STI and provide expertise on STI management. Video/audio recording of dyadic intervention sessions will be used to ensure intervention delivery is consistent with the protocol and to identify content themes to bolster our understanding of relationship dynamics and the potential of communal coping.

Text message boosters related to care-seeking behavior, condom use, and condom access will be provided over the 6 weeks of the study. Messages will be standardized and delivered via an automated 1-way system. No protected health information is disclosed as a part of this communication, but youth will be encouraged to provide an extra layer of protection on existing cell phone security to allow for an additional degree of privacy related to message content. Welcome messages will be sent right after enrollment, “Welcome to the Sexperience study,” followed by 1 text every week, including: “Don’t forget to try out your new communication skills,” “Did you practice the Sexperience role play? Text the # of times you practiced together,” “Condoms prevent STDs. Stop by the clinic if you need some,” “Condoms can improve pleasure, if you need some stop by the clinic,” and “Want to up your game? Practice your condom techniques.” In week 6, we will send “Thanks for trying Sexperience, we’ll call you soon for feedback.”

SMS messages will be sent through TextNow for communicating with participants in both arms of the study. TextNow is one of the fastest growing technology companies with strict policies to protect the user by preventing unauthorized disclosure of information and ensuring physical, electronic, and procedural safeguards are in place according to industry standard procedures and security procedures. Finally, all participants will be encouraged to use standard safety mechanisms such as a pin or password to lock access to their cell phones by others.

Participant dyads in the control group will also receive the 20-minute Focus on the Future for male and Sister-to-Sister for female participants and one-on-one sessions with a gender-matched health educator to guide the patient through skills-based risk reduction counseling. As noted above, these interventions have been evaluated (with African American males and females residing in communities with high STI rates) and were found to increase condom use, reduce unprotected intercourse, and reduce new STIs among participants and are considered effective interventions for clinical implementation by the CDC. Participants in the control arm will also receive positive health-related attention-control text messages focused on general health (healthy eating, exercise, spending time with family and friends, and healthy sleep). No text messages related to relationships or condom use will be sent. As with the intervention group, the message “Thanks for trying Sexperience, we’ll call you soon for feedback” will be sent in 6 weeks. None of these texts will request a response.

COVID-19 Procedure Adjustments

Due to the pandemic, the remainder of participants will be recruited and enrolled virtually. Social media will be used for recruitment, and Zoom videotelephony software will be used to complete the enrollment visit. Recruiters will screen potential recruits over the phone and if eligible, set up a Zoom meeting for enrollment. Participants will be consented with the oral consent script. Recruiters will read the baseline Audio Computer-Assisted Self-Interviewing to the participants and record their answers. There will be separate Zoom meetings for the individual gender-matched intervention, and if the participants are randomized to the intervention group, they will join after for the joint debrief session. The exit survey through Qualtrics will be read to the participants afterward by the recruiters, and their answers will be recorded. Gift cards will be mailed to participants after the enrollment visit has been completed. The 6- to 8-week follow-up survey will remain the same and be completed over the phone with participants.

Outcomes

The primary outcome variable for this pilot study is feasibility of recruitment. Recruitment feasibility will be defined as the number of dyads completing the intervention out of the number of eligible dyads. The feasibility of short-term retention will be calculated as the proportion of enrolled participants who complete a follow-up interview at 6 weeks.

The secondary outcome variable for this pilot study is acceptability, measured as participant satisfaction with their

intervention experience. Participant satisfaction will be measured using a brief survey asking participants to rate their experience with qualitative feedback documented.

Sample Size Determination and Statistical Analysis

A total of 50 adolescent dyads will be enrolled. The choice of 50 dyads is inherently arbitrary and was the number considered realistically feasible to enroll within the limited time of this pilot study. While the study will lack statistical power to detect significant differences in outcomes between the two study arms, point estimates derived from this work will be invaluable for future research proposals to evaluate efficacy. Feasibility and acceptability will be evaluated against benchmarks from previous studies. Observed recruitment rates from the proposed pilot study will be compared to expected recruitment rates (determined from previous studies that recruited adolescents with an STI diagnosis). Prior studies recruiting from the AYA clinic have achieved recruitment rates ranging from 48% to 91%. A similar approach will be used to compare satisfaction scores to an a priori benchmark of patient satisfaction. Based on previous work, average patient satisfaction greater than 80% would be necessary to conclude that the intervention is acceptable. Descriptive statistics will be used to make a comparison of the baseline characteristics between the intervention and control group. Statistical analysis will be based on the standard for randomized controlled trials, and both primary and secondary outcomes for each group will be assessed using an intention-to-treat analysis. Data distribution will be assessed, and comparisons of the 2 groups will be conducted using generalized estimating equations. $P<.50$ will be considered statistically significant. The multiple imputations method will be used to address missing data.

Risks and Ethical Considerations

There are no significant medical risks involved in this study. While the study will attempt to preserve patient confidentiality, there is potential for breaches of confidentiality, but it is miniscule given the limited number of personnel with access to participant information. Finally, while the Sexperience intervention focuses on positive communication and condom negotiation, dyads may experience conflict or disagreement during the context of the joint session. While the health educator will be trained in basic conflict resolution, there are staff onsite to provide both mental health (social work, mental health counselors, psychologists) and seasoned security staff available to intervene as needed. There are no additional risks associated with these telephone calls.

Human subject approval has been granted for beta testing of this research protocol by the Johns Hopkins institutional review board (IRB00083609), and the study was registered at ClinicalTrials.gov [NCT03275168]. All patient data are kept confidential and secure. Individual patient data shared during health education sessions and clinical visits (sexual history data, lab results, clinical findings) will not be disclosed to the partner in accordance with Health Insurance Portability and Accountability Act regulations. However, the patient will be encouraged to notify partners regarding behavioral risks that impact their partner per standard of care and public health practice. The research team on this project has training and experience in the protection of human research participants and the treatment of protected health information. All staff have completed human subjects training through the institution's research compliance training program as a part of orientation training and as a condition of their employment.

Data Safety and Monitoring

The study will use a data safety monitoring plan consistent with National Institutes of Health guidelines. The research team will meet regularly to communicate about ethical issues related to the study. A data safety and monitoring committee was created; members have no formal association with the study and their selection is based on their expertise in AYA clinical interventions, sexual and reproductive health service delivery, and biostatistics.

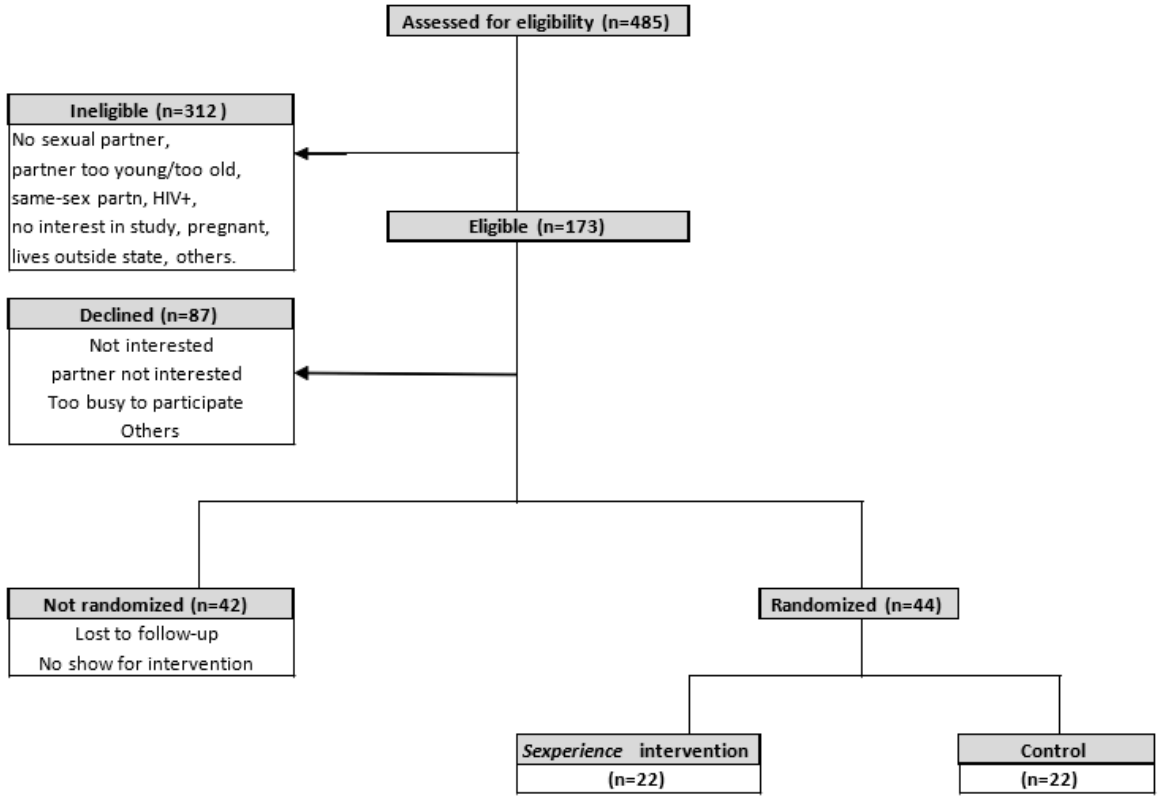
Payment, Remuneration, and Benefits

Study incentives are US $50 for the enrollment visit and US $50 for the 6-week follow-up interview for each participant, both patient and partner. Those participants who elect to complete the in-depth interview will receive an additional US $50. There are no anticipated costs to participants that are unaccounted for in the support and remuneration plan for the study or usual care. Transportation support may be provided for participants with transportation issues. There may be no direct benefits to participants in this study.

Results

Study recruitment began in January 2018 and was initially estimated to be completed in February 2021. As of March 30, 2021, 485 persons were assessed for eligibility, of which 312 (64.3%) were ineligible. Of the 173 eligible participants, 87 (50.3%) declined to participate and 42 (24.3%) were not randomized due to certain factors (Figure 3). So far, 22 dyads (n=44) have been recruited. Of the index patients randomized, most were females (20/22, 91%), with at least a high school diploma (19/22, 86%), and an average of 9 lifetime sexual partners. Index patients and their partners did not differ in age, with mean ages of 21.7 (SD 2.6) years and 22.6 (SD 2.5) years, respectively, and age at first sexual encounter 15.4 (SD 2.5) years and 15.1 (SD 1.8) years, respectively.

Figure 3. Recruitment of study participants.



Discussion

Summary

Preliminary findings from the study show that a dyadic intervention for heterosexual AYA is both feasible and acceptable. To our knowledge, this study will be the first of its kind to engage AYA dyads in a joint STI risk counseling intervention. While many current research studies have used couples engagement for prevention of sexually transmitted diseases, most have focused primarily on HIV to the neglect of other STIs (*Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas vaginalis*), which account for the preponderance of STIs [20,32,33]. Similar studies have been limited to adults or male-male partnerships to the exclusion of younger age groups and heterosexual dyads [9,12,13]. The results from this critical inquiry will further clarify the potential role for a joint health educator–administered sexual education and counseling intervention in enhancing AYA access to sexual and reproductive health services in primary care settings and will determine the feasibility, acceptability, and effectiveness of using the sexually involved dyad as a vehicle for behavioral change. It will also give us an insight into the role of actively engaging sexual partners in joint communications for promoting healthier sexual behaviors on STI prevention compared to the general practice of individualized risk reduction counseling, partner notification, and expedited therapy without mutual engagement [14,17,34]. Dyadic interventions have been used in many medical conditions including parent-adolescent dyads for improving HIV prevention and self-efficacy [35], obesity prevention, and smoking and sedentary lifestyle cessation and were influential for sparking behavior changes [36] and preventing HIV transmission between serodiscordant same-sex male couples. A dyadic intervention for heterosexual couples in Uganda was equally effective for HIV prevention [32].

Consistent condom use and condom negotiation skills reduce STI transmission from an infected partner. Given the high impact of STIs among AYA across the United States, this study will be a first step toward the use of previously untested strategies and a remarkable addition to the current armamentarium in the fight against high STI rates in minority groups and associated sequelae. The study findings will provide new information on more effective ways to engage sexually active AYA in a discussion on sexuality and skills building for a healthier and safer life.

Limitations

The study procedures target African American youth living in an urban community that is currently ranked number 1 in STI rates by the CDC. While we acknowledge that this population may not reflect the distribution of AYA across the United States, the distribution of STI is mirrored in the demographics of study participants. This initial study, although not generalizable to the general US population, is a first step toward larger and more heterogeneous studies.

Since its inception, the study has been modified to accommodate challenges that were not anticipated prior to the launch of the study. One such challenge was the problem with the clause that restricts study recruitment to only persons with a previous or active STI diagnosis. This was met with difficulty in recruiting persons who were otherwise eligible for the study but expressed reluctance in volunteering STI information. Based on the this,

a decision was reached to remove previous (or current) STI as a prerequisite for study enrollment. This modification to the study design was approved by the institutional review board and is consistent with our approach to this exploratory study, and its effect on the speed and ease of recruitment will be evaluated at the end of the study.

Additionally, the current COVID-19 pandemic has been a major hindrance to the recruitment of participants into the study, as recruitment has been conducted through the clinic and via social media advertisements and interventions were previously delivered at in-person clinic visits. In response, the remainder of participants will be recruited and enrolled virtually. Social media will be used for recruitment and Zoom will be used to complete the enrollment visit. Study visits have also been moved to virtual meetings. There will be separate Zoom meetings or rooms for the individual gender-matched intervention and, if the participants are randomized to the intervention group, they will join their partners in the main Zoom room for the joint debrief session. Both participants recruited prior to the onset of the pandemic and during the pandemic will be followed up using phone interviews as designed. The effect of the COVID-19 pandemic on study recruitment or outcomes will be evaluated at the end of the study.

Conclusion

In conclusion, engaging heterosexual urban AYA dyads in a joint intervention for STI prevention and improving self-efficacy for sexual risk reduction is both feasible and acceptable. If successful, the outcome of this study will add to the current literature on the approaches to STI prevention and its success will inform its application in risk reduction counseling for youth who are most at risk for STI in the United States.

Acknowledgments

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Conflicts of Interest

MT receives research supplies from SpeeDx LLC through Johns Hopkins University and serves on the Trojan Sexual Health Advisory Council (Church and Dwight Inc).

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Abbreviations

AYA: adolescents and young adults
BMA: Baltimore (Maryland) metropolitan area
CDC: Centers for Disease Control and Prevention
STI: sexually transmitted infections

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Protocol

Using Smart Displays to Implement an eHealth System for Older Adults With Multiple Chronic Conditions: Protocol for a Randomized Controlled Trial

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Abstract

Background: Voice-controlled smart speakers and displays have a unique but unproven potential for delivering eHealth interventions. Many laptop- and smartphone-based interventions have been shown to improve multiple outcomes, but voice-controlled platforms have not been tested in large-scale rigorous trials. Older adults with multiple chronic health conditions, who need tools to help with their daily management, may be especially good candidates for interventions on voice-controlled devices because these patients often have physical limitations, such as tremors or vision problems, that make the use of laptops and smartphones challenging.

Objective: The aim of this study is to assess whether participants using an evidence-based intervention (ElderTree) on a smart display will experience decreased pain interference and improved quality of life and related measures in comparison with participants using ElderTree on a laptop and control participants who are given no device or access to ElderTree.

Methods: A total of 291 adults aged ≥60 years with chronic pain and ≥3 additional chronic conditions will be recruited from primary care clinics and community organizations and randomized 1:1:1 to ElderTree access on a smart display along with their usual care, ElderTree access on a touch screen laptop along with usual care, or usual care alone. All patients will be followed for 8 months. The primary outcomes are differences between groups in measures of pain interference and psychosocial quality of life. The secondary outcomes are between-group differences in system use at 8 months, physical quality of life, pain intensity, hospital readmissions, communication with medical providers, health distress, well-being, loneliness, and irritability. We will also examine mediators and moderators of the effects of ElderTree on both platforms. At baseline, 4 months, and 8 months, patients will complete written surveys comprising validated scales selected for good psychometric properties with similar populations. ElderTree use data will be collected continuously in system logs. We will use linear mixed-effects models to evaluate outcomes over time, with treatment condition and time acting as between-participant factors. Separate analyses will be conducted for each outcome.

Results: Recruitment began in August 2021 and will run through April 2023. The intervention period will end in December 2023. The findings will be disseminated via peer-reviewed publications.

Conclusions: To our knowledge, this is the first study with a large sample and long time frame to examine whether a voice-controlled smart device can perform as well as or better than a laptop in implementing a health intervention for older patients

with multiple chronic health conditions. As patients with multiple conditions are such a large cohort, the implications for cost as well as patient well-being are significant. Making the best use of current and developing technologies is a critical part of this effort.

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KEYWORDS

eHealth; aged; geriatrics; multiple chronic conditions; chronic pain; smart displays; smart speakers; quality of life; primary care; health expenditures; mobile phone

Introduction

Background

The central question of this project concerns the effectiveness of different media platforms in delivering an eHealth intervention for older adults with multiple chronic conditions (MCCs), including pain. Thus far, eHealth interventions for chronic conditions have generally been delivered through computer websites or smartphone apps. It is unknown whether such interventions could be even more effective for older adults if delivered on emerging smart speakers and display platforms.

Smart speakers, such as Amazon Echo, are voice-controlled devices connected to the internet. Users talk to the device and listen to the results rather than typing and reading. Smart displays, such as Google Nest Hub, offer the same voice interactivity but add a screen to allow for viewing of videos, visual navigation of menu options, and touch selection of options. Both smart speakers and smart displays are increasingly designed to move beyond simple voice commands and responses to offer more conversational interactions via chatbots.

Various authors have speculated about the potential of these devices to transform self-management and treatment of chronic diseases such as diabetes [1-3]. For older adults with ongoing pain, limited mobility, limited vision, or hand tremors, interacting via voice may enhance accessibility. In theory, users could ask questions and have answers immediately spoken back to them. They could hear and respond to messages, request audio services such as guided meditation, record health data, and more just by talking or simple taps on the screen. At the same time, the chatbot interactivity could potentially enhance feelings of relationship and support offered by the device and by the specific eHealth intervention on the device. When asked to predict the near future of voice-activated devices in health care, a Delphi panel of 35 physicians, academics, and information technology specialists predicted that such devices would show notable gains in acceptance and use, particularly among older patients, because of their simplicity of use [4].

Indeed, media reports indicate increasing use of speakers among older adults and people with vision loss, tremors, lack of mobility, and dementia [5-9]. Thus far, a handful of studies, primarily conducted with samples of ≤20, suggest that older adults given smart devices generally report liking them, using them mostly for music and simple information requests such as the weather [10-15]. In a study of 12 older adults given a smart display for 16 weeks, the participants reported finding the device easier to use than a computer [12]. However, they also reported forgetting how to wake up the device, control the volume, or turn it off when it was activated unexpectedly, and device log data showed that one-third of attempted interactions were unsuccessful because the device did not understand the request. However, over time, users showed an increasing ability to rephrase unsuccessful requests, and transcriptions of interactions suggested companionable exchanges between the user and the device.

Thus far, only a couple of pilot studies have focused on health-related uses of smart speakers. In one, 58 patients with chronic conditions were given an Amazon Alexa device for 2 months, and a number of them reported using it to remind them to take their medications and to record when they had done so [16]. In a very similar study, 44 adults aged 50 to 90 years with chronic conditions were given Amazon's Echo Show for 2 months [17]. They too reported using the device for medication and appointment reminders, with additional anecdotes of using it to find recipes tailored to dietary requirements, medication information, exercise videos, guided meditation, or soothing sounds to help with falling asleep. An unspecified subset of users felt that their health and quality of life had improved over the 2 months as a result of the device. Neither study involved a comparison group, reported on actual log data rather than self-reports of use, or systematically assessed health outcomes.

Given these promising small-scale findings, rigorous research seems warranted to examine whether smart displays can facilitate the self-management of chronic conditions. Chronic conditions are prevalent among older adults. Approximately two-thirds of Medicare beneficiaries have ≥3 ongoing conditions such as diabetes or arthritis, and nearly one-fourth have ≥5 [18,19]. The complexity of patients' comorbidities makes them challenging to serve well in primary care, where time pressures and patient loads necessitate a focus on medication and laboratory results rather than well-being and skills for self-management, treatment adherence, and health tracking [20]. Patients with MCCs are also the most expensive, accounting for 90% of Medicare spending [18]. Most important for the individual patient, having multiple conditions is associated with reductions in physical and psychosocial quality of life [21-23] and increased risk of chronic pain [24].

Chronic pain, generally defined as pain lasting ≥3 months, is reciprocally intertwined with a number of variables [25] such as anxiety and depression [26,27], sleep [28], and daily functioning [29]. Chronic pain also intersects with issues of

social justice; a recent review noted that those with lower socioeconomic status are more likely to report chronic pain, more severe pain, and more pain-related disability [24]. Various meta-analyses have indicated ongoing racial disparities, such that African Americans and other patients of color tend to be undertreated for pain [30,31]. Increased self-management of chronic pain is a national objective established by the US Department of Health and Human Services in *Healthy People 2030* for the next decade [32], and there is evidence that internet-based interventions can improve pain-related outcomes [33-35]. However, no research thus far has examined self-management interventions for chronic pain within the context of MCCs. Furthermore, there is no research on the relative effectiveness of different platforms for delivering such an intervention for this complex patient population.

Need for a Trial

Large-scale, long-term trials of the effectiveness of delivery platforms may help advance the objective outlined in *Healthy People 2030*. This paper reports on the study design and methods of a randomized controlled trial of the effectiveness of an evidence-based eHealth intervention for older adults with MCCs, including pain, when delivered on a smart display versus a laptop platform.

The system, ElderTree, was developed by our Agency for Healthcare Research and Quality Center of Excellence in Active Aging to improve quality of life and socioemotional outcomes among older adults and was first tested in a randomized controlled trial involving 390 older adults who were followed for 12 months. In that intention-to-treat trial, patients in the ElderTree group who had had ≥3 primary care visits in the 6 months before baseline showed significantly better results on measures of mental quality of life, social support, and depression compared with control patients who had received a laptop but no ElderTree access [36].

Given that primary care use is relatively high among patients with MCCs, the results suggest that ElderTree may most benefit such patients and may be most effective if integrated into primary care. A subsequent randomized controlled trial, funded by the National Heart, Lung and Blood Institute, is currently testing ElderTree among patients with MCCs, with an added report to primary care clinicians documenting changes in health status. That ongoing trial is testing whether patients assigned to a laptop-based ElderTree versus an attention control will have better quality of life, fewer symptoms, and better condition-specific laboratory scores [37].

The trial described in this protocol is designed to test whether the delivery platform of the intervention affects its effectiveness. Specifically, the study aims to assess whether participants using ElderTree on a smart display will experience decreased pain interference and improved quality of life and related measures in comparison with participants using ElderTree on a laptop and control participants given no device or access to ElderTree.

Methods

Trial Design

The trial has a randomized controlled design with 3 groups with 1:1:1 allocation. Participants will be randomized to receive (1) a smart display plus internet access plus ElderTree along with their usual care, (2) a touch screen laptop plus internet access plus ElderTree along with their usual care, or (3) usual care alone. All participants will be followed for 8 months.

Sample Size and Study Setting

A total of 291 older adults will be recruited from the University of Wisconsin–Madison Department of Family Medicine and General Internal Medicine system (UW Health), Access Community Health Centers, and community organizations in the Madison and Beloit, Wisconsin, areas.

Intervention Groups

Control

Participants in the control arm will continue with their usual care and receive no device or intervention from the study.

ElderTree on a Smart Display Platform

In addition to continuing with their usual care, participants in the ElderTree on a smart display platform (ET-SD) arm will receive access to ElderTree for 8 months plus a Google Nest Hub Max smart device and internet access. The device consists of a voice-activated smart speaker and a 10-inch visual display that is optionally touch-activated.

ElderTree on a Laptop Platform

In addition to continuing their usual care, participants in the ElderTree on a laptop platform (ET-LT) arm will receive access to ElderTree for 8 months plus a touch screen laptop computer and internet access.

Eligibility Criteria

Eligible participants will (1) be aged ≥60 years and (2) have chronic pain as indicated by having received a chronic pain diagnosis or reporting pain on some or most days that has lasted for ≥12 weeks (duration); reporting pain in the last 3 months on some, most, or all days (frequency); and reporting a pain intensity of ≥3 on a scale of 0 (no pain) to 10 (worst imaginable pain) in the last 7 days. They will also (3) have at least 3 of the most prevalent chronic conditions among older adults as reported by the Centers for Medicare and Medicaid Services [18]: chronic obstructive pulmonary disease, asthma, diabetes, hyperlipidemia, hypertension, ischemic heart disease, atrial fibrillation, heart failure, stroke, cancer, chronic kidney disease, depression, osteoporosis, and arthritis; we have modified the list by adding obesity (BMI≥30) and dizziness, falls, and loss of vestibular function. In addition, patients (4) will allow reports to their primary care provider about their health tracking and (5) should have no plans to leave during the study period. Patients are not eligible if they require an interpreter or if they have a medical diagnosis of Alzheimer disease, dementia, schizophrenia or other psychotic disorder, autism spectrum disorder, known terminal illness with <6 months to live, or an acute medical problem requiring immediate hospitalization.

Recruitment

For UW Health recruitment, the university's Clinical and Health Informatics Institute will use clinic records to identify patients meeting the aforementioned eligibility criteria and send their name, address, birthdate, age, UW Health clinic location, and primary care physician to the university's Office of Clinical Trials via REDCap (Research Electronic Data Capture; Vanderbilt University). Potential participants will receive an opt-in letter describing the study and consent form from the Office of Clinical Trials plus a stamped return letter inviting contact from the study team.

We will supplement recruitment at UW Health with community efforts to increase the racial diversity of our patient population. The selection of and engagement with community organizations will be led by a senior advisor on our team with extensive experience in local health campaigns and deep roots in the local African American health care and patient communities. Through collaborations with the African American Health Network, Rebalanced-Life Wellness Association, African American Opioid Coalition, and the Community-Academic Aging Research Network, we will reach out to Black churches, community centers, fraternity and sorority health service programs, and other organizations as selected by our advisor in the Madison and Beloit areas of Wisconsin. We will distribute a recruitment flyer and consent form with a return card or opt-in and conduct video chat and in-person community sessions when possible to introduce the study and invite participation.

Through Access Community Health Centers, we expect to reach a larger number of African Americans and other participants of color as well as expand our reach to underserved patients. We will work directly with Access Centers staff to disseminate the recruitment flyer, consent form, and return card or opt-in to potential patients.

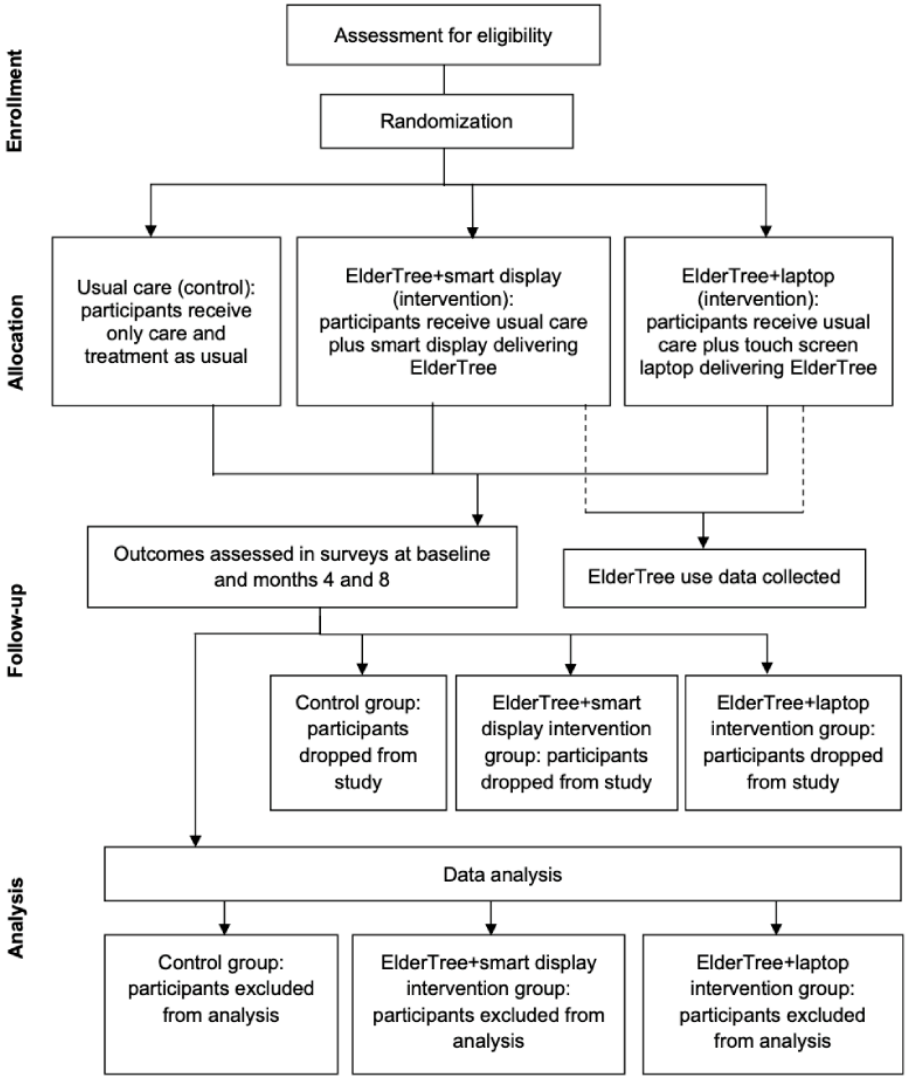
Regardless of the recruitment method, when a return card or opt-in is received, study staff will call and assess eligibility; provide a study overview that includes potential benefits and risks, study procedures, and compensation; thoroughly walk through informed consent; and address questions. The baseline survey will be mailed. Patients will be given adequate time to decide whether to participate and, in some cases, a follow-up phone call will be scheduled after the patient has had time to review the survey and consent form.

Once a patient verbally confirms that they want to participate, a home visit will be scheduled to collect the baseline survey, randomize, set up the equipment, and train. All study staff who conduct home visits will be fully vaccinated against COVID-19, wear face masks, and socially distance as much as possible while in the patient's home. If no visit is desired, the equipment will be shipped once the study staff receives the completed baseline survey via mail, and technology setup and training will be conducted by phone. The baseline survey should take 20 to 30 minutes. The measures will be the same in all 3 arms to avoid differential dropout. We will document those who choose not to participate and why following the CONSORT (Consolidated Standards of Reporting Trials) guidelines.

Randomization

Once informed consent and the baseline survey have been obtained from patients, the project manager will use a computer-generated allocation sequence to randomize on a 1:1:1 ratio to the ET-SD, ET-LT, or control group stratified by sex (male or female), site (UW Health, Access Centers, or the community), and number of chronic conditions (≤5 or ≥6). A research staff member will then conduct equipment setup and training for patients based on group assignment, which is provided in a sealed opaque envelope. Obviously, once an assignment is made and a device has been set up, participants cannot be blinded to their condition. To set up participants on their assigned system (ET-SD or ET-LT), the researcher conducting the training cannot be blinded to the condition after assignment. Figure 1 shows the flow of participants during the trial.

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram.



Timeline

Textbox 1 shows the timeline by year of the study, with year 1 beginning in August 2020 and year 5 ending in July 2025.

Textbox 1. Timeline of project activities.

Timeline and activities

- Year 1, months 1 to 9: pilot-test smart display and complete development, develop content plan for laptop and smart display, prepare and finalize study and data collection materials
- Year 1, months 6 to 9: data quality monitor plan
- Year 1, months 7 to 9: receive institutional review board approvals, train research staff
- Year 1, month 7, to year 4, month 5: create and refresh content
- Year 2, month 1, to year 3, month 9: recruit, pretest, and randomize patients
- Year 2, month 1, to year 4, month 5: collect quantitative and qualitative data
- Year 2, month 9, to year 4, month 12: clean and prepare data
- Year 2, month 9, to year 5, month 12: analyze results
- Year 3, month 12, to year 5, month 12: publish

Intervention

Background

For more than 30 years, our center has been developing and testing an evolving suite of eHealth systems collectively known as the Comprehensive Health Enhancement Support System (CHESS). ElderTree is one of these systems. All CHESS systems are built on principles of continuing care and self-management: long duration [38]; assertive outreach [39]; tracking [40]; prompts [41]; action planning [42]; problem solving and self-tailoring [43]; peer, family, and clinical support [44]; and care coordination [45]. In randomized trials, CHESS systems have significantly improved asthma control [46]; quality of life and cost of care in patients with HIV [47]; quality of life and self-efficacy in patients with breast cancer, including older women [48], compared with control [49] and internet [50] groups; risky drinking [51]; and caregiver burden, symptom distress, and median length of survival in patients with lung cancer [52].

System Overview

ElderTree is designed for older adults and with their input to offer tools, motivation, and social support for helping patients manage chronic pain and other chronic conditions. As reported in previous and ongoing studies of ElderTree [36,37], the laptop system is a members-only website free of advertisements with design features based on older users' feedback as well as best practices for older populations, such as larger fonts, fewer options, and uncluttered screens for better comprehension, navigation, and usability [53]. The newly developed ET-SD version adheres to the same principles of effective interventions and system design (eg, uncluttered screens and fewer options) for older adults. Both systems substantially replicate ElderTree as described in our ongoing study comparing ET-LT with an attention control [37], with modifications and enhancements to focus on chronic pain and align with the technical capabilities of the smart platform.

Theoretical Foundation

ElderTree and other CHESS systems are consistent with self-determination theory, which asserts that satisfying 3 basic psychological needs contributes to adaptive functioning: competence (feeling effective, not overwhelmed), social relatedness (feeling connected to others, not isolated), and intrinsic motivation (feeling autonomous, not coerced) [54].

Interface and Features

The key features of the site and how they align with self-determination theory are described in Table 1.

Table 1. Key features and theoretical basis of the ElderTree eHealth intervention.

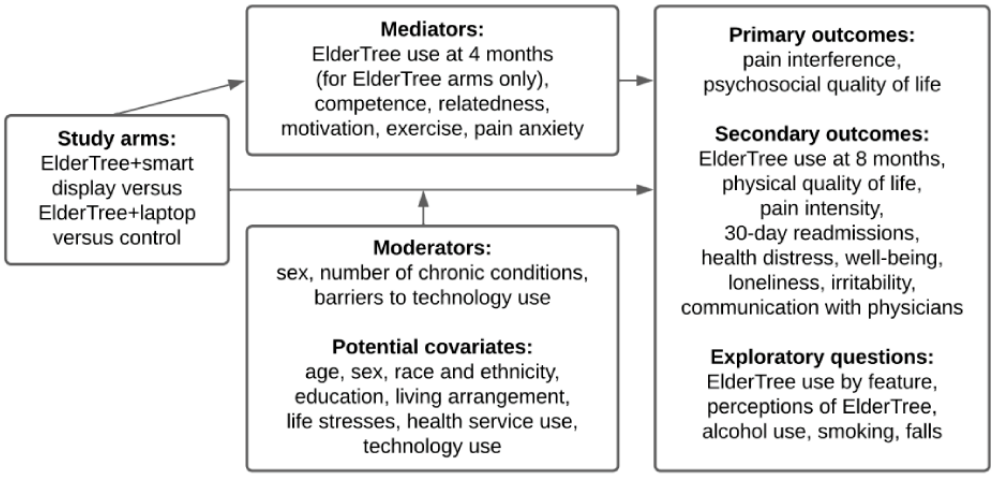
Feature or function	Description	Self-determination theory construct
Living Well with Chronic Pain course	Eight 20-minute learning modules with the latest findings on pain and evidence-based coping strategies	Health-related coping competence; motivation
Health library and wellness activities	Relaxation, meditation, physical exercise (eg, chair yoga), activity, and informational videos in relevant topic areas	Health-related coping competence; motivation
Weekly survey and clinician report	Tracking of self-reported general health measures (eg, sleep, mood, and exercise), graphed over time available for patients and their primary care clinicians	Health-related coping competence; motivation
Discussion groups (all)	Monitored support and chat forums [55,56]	Social relatedness and support
Chronic pain discussion group	Participants' shared tips, experiences, and resources for managing chronic pain [57]	Health-related coping competence; social relatedness and support; motivation
Journal	Interactive function with prompts based on positive psychology principles [58]	Health-related coping competence; motivation
Thought of the day	Daily motivational and inspirational prompts	Motivation
Comment functionality	Posting function to promote engagement and relationship building on all information and activity pages	Social relatedness and support
Notifications and reminders	Custom reminders to take the weekly survey of health indicators; email and system notifications of responses to the user's posts	Health-related coping competence

Outcomes and Variables

Primary Outcomes

Figure 2 illustrates the study logic. Our primary outcome is the differences between patients in the ET-SD arm, patients in the ET-LT arm, and control patients in pain interference and psychosocial quality of life.

Figure 2. Study logic.



Secondary Outcomes

There are several secondary outcomes. First, we will determine whether ET-SD, relative to ET-LT, increases participants' use of the intervention at 8 months. The original trial of ElderTree found high and sustained engagement relative to reports for other health apps [36]. Nonetheless, many participants did not use it extensively, a problem shared by all digital apps [59-62]. Thus, overcoming barriers to sustained, in-depth use is a critical challenge. This study is designed to investigate whether the voice-controlled interface, relative to the laptop, increases adoption and sustains the use of the intervention, thereby improving its effects on quality of life and health outcomes.

Outcomes also include differences between all 3 groups on measures of physical quality of life, well-being, communication with health care providers, pain intensity and duration, 30-day hospital readmission rates, health distress, loneliness, and irritability. In addition, we will compare ET-LT with the control group, given the unique focus on chronic pain in this study.

Exploratory Questions

We will measure the level of use of each ElderTree feature in both platforms and assess use differences between the 2 ElderTree arms as well as participants' perceptions of the intervention. Differences between the ET-SD, ET-LT, and control groups on alcohol use, smoking, and falls will also be explored.

Mediation

For the 2 ElderTree arms, we will investigate whether the effects of study arm on changes from baseline to end point in primary and secondary outcomes are mediated by use of the intervention at the 4-month midpoint. For all study arms, we will also investigate whether feelings of competence, social relatedness, and intrinsic motivation as well as exercise and pain anxiety mediate the effects of the arm on all outcomes.

Moderation

We will investigate whether the effects of study arm on changes from baseline to end point in primary and secondary outcomes are moderated. That is, analyses will test whether the benefits of smart displays (vs laptops) vary by participant sex (women will show more benefit than men), number of chronic conditions (patients with more conditions will show more benefit), and number of barriers to using technology (those with fewer barriers will show more benefit).

Potential Covariates

We will consider a number of covariates: age, sex, race and ethnicity, education, living arrangement, life stresses, health service use, and technology use. Of this list, those variables that significantly predict our primary outcomes and improve the overall model's Akaike information criterion will be included in the final analysis.

Measures

Overview

Table 2 lists all planned variables and their measures. Scales have been selected to have good psychometric properties with similar populations. Patient-reported measures, including modifications to validated scales, are described following the table.

Table 2. Measures used to evaluate ElderTree on a smart display platform versus ElderTree on a laptop platform versus control.

Variable	Measure	Survey questions, N	Source	Psychometrics
Primary outcomes				
Pain interference	PROMIS-29[a]	4	Patient	α range ≥.88 [63]
Psychosocial quality of life	PROMIS-29	12	Patient	α range ≥.90 [64]
Secondary outcomes				
ElderTree use at 8 months	Number of log-ons	N/A[b]	ElderTree	N/A
Physical quality of life	PROMIS-29	12	Patient	α range ≥.90 [64]
Pain intensity	PROMIS-29	3	Patient	α range ≥.90 [64]
30-day readmissions	Number of admissions	1	Patient	N/A
Health distress	Lorig Health Distress Scale	4	Patient	α=.87 [65]
Well-being	WHO[c] Well-Being Index	5	Patient	α=.93 [66]
Loneliness	NIH[d] Toolbox	5	Patient	α=.93 [67]
Irritability	Brief Irritability Test	5	Patient	α range ≥.88 [68]
Communication with physicians	Lorig Communication with Physicians	3	Patient	α=.89 [65]
Exploratory questions				
ElderTree feature use	Number of page views per feature	N/A	ElderTree	N/A
ElderTree perceptions	Created for study; Lund	12	Patient	α=.91 [69,70]
Alcohol use	Alcohol Use Disorders Identification Test	3	Patient	α=.69-.91 [71]
Smoking	Number of cigarettes per day	1	Patient	N/A
Falls	Number of falls in last 6 months	2	Patient	N/A
Mediator candidates				
ElderTree use at 4 months	Number of page views	N/A	ElderTree	N/A
Competence	Self-Efficacy for Managing Chronic Disease	6	Patient	α=.91 [72]
Relatedness	McTavish Bonding Scale	5	Patient	α=.85 [50]
Motivation	Treatment Self-Regulation Questionnaire	4	Patient	α=.85 [73]
Exercise	Created for study	4	Patient	N/A
Pain anxiety	Pain Catastrophizing Scale	13	Patient	α=.87 [74]
Moderator candidates				
Sex	Sex	1	Patient	N/A
Chronic conditions	Total number of conditions	16	Patient	N/A
Barriers to technology use	Created for study	2	Patient	N/A
Potential covariates				
Demographics	Age, sex, race and ethnicity, education, and living arrangement	6	Patient	N/A
Other	Life stresses, health service use, and technology use	3	Patient	N/A

[a]PROMIS-29: Patient-Reported Outcomes Measurement Information System–29.

[b]N/A: not applicable.

[c]WHO: World Health Organization.

[d]NIH: National Institutes of Health.

Primary and Secondary Outcomes

Pain interference will be assessed using 4 items from the Patient-Reported Outcomes Measurement Information System (PROMIS-29) global health measure (version 2.1) [63,64] asking how much the patients' pain has interfered with day-to-day activities, work around the home, ability to participate in social activities, and household chores. Psychosocial quality of life

will be assessed using 12 PROMIS-29 items asking about anxiety, depression, and the ability to participate in various roles and activities.

ElderTree use at 8 months will be measured by the number of log-ons to the system. Physical quality of life will be assessed using PROMIS-29 items asking patients to rate physical functions such as ability to do chores and use stairs, fatigue, and sleep quality over the last 7 days. Pain intensity will be measured using a PROMIS-29 item on average intensity of pain in the last week and an item from Lorig on intensity of pain at its worst over the last 7 days. An additional item from Lorig will ask about the duration of pain over the last 7 days [65]. Participants will report 30-day hospital readmissions for or as a consequence of the same problem within the last 4 months. Health distress (discouragement, fear, worry, and frustration regarding health and health problems) will be measured using the Lorig Health Distress Scale [75]. Well-being in the last 7 days will be measured using 5 items from the World Health Organization Well-Being Index [66]; loneliness will be measured using 5 items from the National Institutes of Health Toolbox Social Relationship Scale, Loneliness subscale [76]; and irritability in the last 7 days will be measured using the 5-item Brief Irritability Test [68]. Finally, communication with health care providers will be assessed using the Lorig Communication with Physicians measure [75].

Exploratory Questions

ElderTree use data, including features used and duration of use, will be collected automatically. At baseline, 4 months, and 8 months, patients will report on alcohol use in the last 4 months with 3 consumption items from the Alcohol Use Disorders Identification Test [71] and on smoking with average number of cigarettes per day. At baseline and 8 months, falls will be assessed with 2 items asking how often the participant has fallen in the last 6 months and how many falls required medical attention. A fall is defined in the survey as “the body going to the ground without being pushed.” Finally, for the purposes of future development, participants in the 2 ElderTree groups and clinicians will be asked about their perceptions of the system.

Mediation

ElderTree use at 4 months will be measured as the number of page views per service. Feelings of competence will be assessed using the 6-item Self-Efficacy for Managing Chronic Disease scale, which asks about patients’ confidence in, for example, keeping “fatigue caused by your conditions from interfering with the things you want to do.” The time frame and ranking scale of the questions will be modified to align with our other ranked measures and the timing of the patient surveys [72,77]. Relatedness will be assessed with the 5-item McTavish Bonding Scale, in which patients indicate the frequency of particular types of support such as “someone you can count on to listen to you when you need to talk” [78]. Motivation will be assessed using 2 items from the autonomous subscale and 2 items from the external regulation subscale of the Treatment Self-Regulation Questionnaire (eg, “I tried to manage my health conditions because I feel pressure from others to do so”) [79]. Participants will respond to 4 items asking about the amount of aerobic, stretching and flexibility, strength, and balance exercises performed per week. For pain anxiety, patients will rank 13 items from the Pain Catastrophizing Scale [74].

Moderation

The patients will indicate their sex. For barriers to technology use, they will indicate the degree of difficulty they have with computers, tablets, and smart speakers as a result of poor vision, poor hearing, problems vocalizing, lack of knowledge, memory problems, and a custom *other*. The total number of chronic conditions will be determined by the participants responding *yes* or *no* to a list of common conditions [18] during eligibility screening and on the 4- and 8-month surveys. Each time point’s count will be used as the moderator for the effect of study arm at that time point.

Potential Covariates

Participants will report their age, sex, race and ethnicity, education level, and living arrangement at baseline. At baseline, 4 months, and 8 months, they will complete checklists of life stresses in the last 4 months, health services used in the last 4 months, and technology use in the last 4 months.

Data Analysis

Our primary outcome used to power the study is reduction in pain interference. On the basis of PROMIS validation studies with chronic pain samples, a difference of ≥3 points between study arms was considered to indicate a clinically meaningful difference [80]. The PROMIS website also provides the mean and SD of the *T*-score metric (mean 50, SD 10). We powered the analysis to be able to detect a 3-point difference (an effect size of d=0.30) between the control and ET-LT groups, and then the same magnitude of effect between the ET-LT and ET-SD groups (an effect size of d=0.60 for control vs ET-SD). Across 10,000 linear mixed model simulations, a postattrition N=255, we would have power of >80% to detect the study arm × time interaction. In a previous ElderTree trial, 353 (90.5%) of 390 participants completed the 6-month survey, and 310 (79.5%) of 390 completed the 12-month survey [36]. In the completed surveys, data were missing for approximately 2% of the core items. We expect similar rates in this study, or approximately 87% survey completion at 8 months. Thus, we increased the total sample size after attrition to 291 to increase the likelihood of detecting effects on the outcomes with 2 moderators: sex and number of chronic conditions.

Data Collection Methods

Patient Surveys

The following patient-reported measures will be gathered via participant surveys at baseline, 4 months, and 8 months: psychosocial quality of life, physical quality of life, pain, 30-day hospital readmissions, health distress, well-being, loneliness, irritability, communication with physicians, alcohol use, smoking, falls, barriers to technology use, life stresses, health service use, technology use, competence, relatedness, motivation, exercise, and pain anxiety. At 4 and 8 months, participants will respond to the same checklist of common chronic conditions, including pain, that they answered at eligibility screening. Demographics will be gathered only at baseline. The baseline, 4-month, and 8-month surveys containing

all questions posed to participants are provided in Multimedia Appendix 1.

Surveys will be mailed to patients in all groups with a self-addressed stamped envelope and will take 20 to 30 minutes to complete. Patients will be phoned if they do not respond after 2 weeks. Patients can contact the study staff for more details if questions arise. Contact with patients can be requested by the staff if data integrity or compliance issues are detected in the ongoing data review. Survey data will be entered into REDCap. Participants in the 2 ElderTree arms will be paid US $10 to complete each of the 3 surveys (US $30 in total), and those in the control group will be paid US $30 to complete each of the 3 surveys (US $90 in total).

ElderTree System Data

Data from the ElderTree weekly survey will be used to assess medication adherence; falls; thinking and memory; mood; healthy meals, snacks, and drinks; physical activity; quality time with others; sleep; pain; and balance. For the ElderTree system use outcomes, keystrokes for ET-LT, voice commands for ET-SD, and time on the system will be collected continuously. Data on ElderTree use in both arms will be collected in time-stamped log files. The primary measure of use will be log-ons per week. Additional use measures will be number of ElderTree features used, pages viewed, messages posted, and weekly surveys completed.

Qualitative Interviews

Interviews will be conducted using prepared scripts by people unaffiliated with the study, trained and monitored by one of the co–principal investigators (MLM). Data will be gathered from 32 patients, 16 (50%) in each of the 2 ElderTree arms, balanced by clinic versus community recruitment site and by number of chronic conditions (≤5 vs ≥6). Half of each group will be interviewed at 4 months, and the other half will be interviewed at 8 months. This balances the need for insight into patient experience with the need to avoid confounding interview effects with ElderTree effects. They will be asked about insights critical to the ultimate dissemination of interventions such as ElderTree: barriers to use, technical issues that arose, whether and how ElderTree fit into their day, what could be done to make ElderTree better, reactions to the device, and whether and how ElderTree came up in appointments with their physician.

Interviews are expected to last 30 to 60 minutes and are based on a standard set of questions, although clarification questions may vary. Potential participants will be contacted by ElderTree system messaging or by phone. All interviews will be transcribed for more detailed coding, including quantitative tagging of key concepts.

Clinicians will encounter ElderTree only through the clinician report. We will record and analyze clinicians' comments and questions during meetings where we introduce the study and the clinician report to the clinics, and we will ask about anticipated barriers and benefits. We will document the protocols that clinics use to receive and disseminate the report to clinicians. We will interview 5 clinicians at the end of data collection about their experiences with and perceptions of the report. Interviews are expected to last 10 to 20 minutes and are based on a standard set of questions, although clarification questions may vary.

Retention

We will promote retention by providing ready access to support for patients' use of the technologies and by actively following up with patients to encourage them to return surveys. If a survey is not returned within 2 weeks, a research team member will call to check that the survey was received and encourage the patient to complete and return it in the addressed stamped envelope. The date and time of the phone call will be recorded in REDCap along with whether the researcher talked to the participant directly or left a message and any information gathered during the phone conversation. If we cannot reach the participant, another copy of the survey will be sent with a personal note asking them to complete it or call us on our toll-free number if they have questions or are no longer interested. In our study of older adults with MCCs, for which we have recently completed data collection, survey response rates were 94.7% at 6 months, 93.6% at 12 months, and 92.3% at 18 months [37].

Data Management

To mitigate the risk of breaches of patient confidentiality, all participants are assigned a unique code number. All contact information and survey data are housed electronically in REDCap. Survey data are double-entered by 2 different individuals to ensure accuracy. Paper-based files are stored in a locked room in locked file cabinets and can be accessed only by authorized personnel. The database administrator provides access to study data at appropriate levels for various members of the research team. Members of the research team are able to view deidentified individual and clinic-level aggregations of the variables.

Statistical Methods

Predictor Assumptions

Successful randomization of participants will be tested based on sex, recruitment site (UW Health, Access Centers, and the community), and number of chronic conditions. If randomization fails for any of these variables, it will be added as a covariate in subsequent analyses. We will test to see if the nesting structure of recruitment site significantly influences our findings. If data cannot be pooled across sites, site will be addressed either by multilevel modeling or by treating recruitment site as a moderator, depending on the analyses being run.

Outcome Assumptions

Normality, linearity, and homoscedasticity and homogeneity of variance for the outcome data will be assessed using descriptive statistics and graphical representations. Data transformation, linear mixed models, or nonparametric tests will be used to deal with assumption failures of the outcome data.

Missing Data

In previous work with older adults using ElderTree, we kept the missing data on core interview items to approximately 2%; we expect similar rates in this study. In primary care, data are

not likely to be missing at random; that is, the probability that data are missing relates to what the data would have been had the data been observed. We will conduct a sensitivity analysis on missing data using logistic regression to examine whether dropout at follow-up is associated with observed or assigned factors, covariates, or outcomes at baseline [81]. If missing data affect power or are significantly not missing at random, linear mixed models or multiple imputation will be used [82]. If patients drop out, we will not use any of their data beyond their withdrawal date. Data before the withdrawal date will be included in the intention-to-treat analysis.

Effectiveness of Control Versus ET-LT Versus ET-SD

Linear mixed-effects models, which account for dependence among successive observations for the same participant and can address incomplete data, will be used to examine the effects of study arm (ET-SD vs ET-LT vs control, a between-participant factor) on our outcomes over time. We will conduct specific treatment×time contrasts both between and within groups to test time-based effects. For binary, count, and other nonnormal data, generalized mixed-effects models will be used.

Mediation and Moderation Effects

Structural equation modeling will explore the effects of mediation on the relationship between study arms and our 2 primary outcomes. We anticipate that the impact of study arm on pain interference and psychological quality of life will be mediated by our theoretical constructs of competence, relatedness, and motivation; exercise; and pain anxiety at 4 months. Structural equation models involving ElderTree use will be run separately only for the ET-SD and ET-LT arms. We anticipate that sex, number of chronic conditions, and barriers to technology use will moderate the indirect paths of the mediation models.

Impact of Interim Analyses on Type 1 Error for Whole-Sample Analysis

Findings that are significant in the interim but not the final analyses will be treated as nonsignificant. The final analysis will examine all data over time. For analyses that address the same hypothesis, a Holm–Bonferroni correction will be applied.

Qualitative Analysis

For data sets of patient and physician interviews, a coding scheme of key themes will be constructed based on the research questions of perceived benefits and barriers to use and examination of the data. Each scheme will be pilot-tested, and then 2 trained coders will code an overlapping subsample of 20% of content. Once reliability is established with a minimum Krippendorff α of .80 per category, the coders will work independently to code the rest of the material.

Ethics Approval

This study protocol received ethical approval from the University of Wisconsin Health Sciences and Minimal Risk Research Institutional Review Board (reference 2020-0868). All amendments to the protocol have been submitted to the institutional review board and approved. This study complies with the Declaration of Helsinki and its later amendments.

Results

Recruitment began in August 2021 and will run through April 2023. The intervention period will end in December 2023. As of March 21, 2022, a total of 109 participants have been recruited. The findings will be disseminated via peer-reviewed publications.

Discussion

Study Overview

To our knowledge, this is the first study to examine with a large sample and a long time frame whether a smart device can, in reality, perform as well as or better than a laptop in implementing a health intervention. To assess this, we will examine group differences in pain and quality of life measures among patients in high need of resources to help manage their chronic conditions. A 2021 systematic review of research on the use of "voice-based conversational agents for the prevention and management of chronic conditions" concluded that the field is "in its infancy" [83].

Comparison With Prior Work

Our center is well-positioned to pursue this question as we have an evidence-based laptop system available for adaptation and comparison. The results of our first trial of ElderTree indicated that older patients coping with multiple comorbidities were most likely to benefit from such an intervention [36], and our subsequent study is testing that hypothesis [37]. The study described in this protocol, targeting similar patients, is designed to test and compare how delivery platform affects pain and psychosocial variables that have shown improvement with the laptop version [36]. Comparing platforms with this highly challenged population may highlight more starkly the relative advantages and pitfalls of voice-controlled platforms for eHealth delivery.

Future Directions

Applications for voice-controlled devices are in the early stages of development. Some known limitations, such as problems with dictation and word recognition, are certain to improve. Others, including the lack of ability to review longer lists of results or read larger amounts of text, may be endemic. Still other limitations, as yet unknown and coming to light as developers stumble upon them, may or may not be resolved. Whether the advantages of the technology outweigh the disadvantages and how its unique capabilities may be optimized, if at all, are empirical questions to be explored in this and future studies.

A specific question is whether smart devices for eHealth may be more effective depending on the health context. For example, this protocol describes an intervention targeting chronic pain. We are also in the system development stage of a trial of smart devices funded by the National Heart, Lung and Blood Institute in which the primary outcome is functional health, a variable that includes multiple physical and psychoemotional factors.

Conclusions

The goal of ElderTree, regardless of delivery platform, is to improve patient self-management and provide convenient, ongoing support as a means to improve health and quality of life. At the same time, and as a result, interventions such as ElderTree may help relieve some of the burden on the primary health care system. As older patients with MCCs are such a large and growing cohort, the implications for access and cost as well as patient well-being are significant. Making the best use of current and developing technologies is a critical part of this effort.

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Conflicts of Interest

DHG Sr has a small shareholder interest in CHESS Health, a corporation that develops health care technology for patients and family members struggling with addiction. This relationship is managed by DHG Sr and the Conflict of Interest Committee of the University of Wisconsin–Madison.

Multimedia Appendix 1
Baseline, 4-month, and 8-month patient surveys.
[PDF File (Adobe PDF File), 913 KB - resprot_v11i5e37522_app1.pdf]

Multimedia Appendix 2
Peer review from NCI-J - Healthcare Information Technology Research [HITR] Study Section, Agency for Healthcare Research and Quality (Agency for Healthcare Research and Quality, USA).
[PDF File (Adobe PDF File), 91 KB - resprot_v11i5e37522_app2.pdf]

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Abbreviations

CHESS: Comprehensive Health Enhancement Support System
CONSORT: Consolidated Standards of Reporting Trials
ET-LT: ElderTree on a laptop platform
ET-SD: ElderTree on a smart display platform
MCCs: multiple chronic conditions
PROMIS-29: Patient-Reported Outcomes Measurement Information System–29
REDCap: Research Electronic Data Capture
UW Health: University of Wisconsin–Madison Department of Family Medicine and General Internal Medicine system

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Proposal

A Scalable Service to Improve Health Care Quality Through Precision Audit and Feedback: Proposal for a Randomized Controlled Trial

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Abstract

Background: Health care delivery organizations lack evidence-based strategies for using quality measurement data to improve performance. Audit and feedback (A&F), the delivery of clinical performance summaries to providers, demonstrates the potential for large effects on clinical practice but is currently implemented as a blunt *one size fits most* intervention. Each provider in a care setting typically receives a performance summary of identical metrics in a common format despite the growing recognition that *precisionizing* interventions hold significant promise in improving their impact. A precision approach to A&F prioritizes the display of information in a single metric that, for each recipient, carries the highest value for performance improvement, such as when the metric's level drops below a peer benchmark or minimum standard for the first time, thereby revealing an actionable performance gap. Furthermore, precision A&F uses an optimal message format (including framing and visual displays) based on what is known about the recipient and the intended gist meaning being communicated to improve message interpretation while reducing the cognitive processing burden. Well-established psychological principles, frameworks, and theories form a feedback intervention knowledge base to achieve precision A&F. From an informatics perspective, precision A&F requires a knowledge-based system that enables mass customization by representing knowledge configurable at the group and individual levels.

Objective: This study aims to implement and evaluate a demonstration system for precision A&F in anesthesia care and to assess the effect of precision feedback emails on care quality and outcomes in a national quality improvement consortium.

Methods: We propose to achieve our aims by conducting 3 studies: a requirements analysis and preferences elicitation study using human-centered design and conjoint analysis methods, a software service development and implementation study, and a cluster randomized controlled trial of a precision A&F service with a concurrent process evaluation. This study will be conducted with the Multicenter Perioperative Outcomes Group, a national anesthesia quality improvement consortium with >60 member hospitals in >20 US states. This study will extend the Multicenter Perioperative Outcomes Group quality improvement infrastructure by using existing data and performance measurement processes.

Results: The proposal was funded in September 2021 with a 4-year timeline. Data collection for Aim 1 began in March 2022. We plan for a 24-month trial timeline, with the intervention period of the trial beginning in March 2024.

Conclusions: The proposed aims will collectively demonstrate a precision feedback service developed using an open-source technical infrastructure for computable knowledge management. By implementing and evaluating a demonstration system for precision feedback, we create the potential to observe the conditions under which feedback interventions are effective.

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KEYWORDS

learning health system; audit and feedback; anesthesiology; knowledge-based system; human-centered design

Introduction

Background

There is nearly universal agreement regarding the need to improve care quality and health outcomes. All health care delivery organizations measure care quality and outcomes, increasingly via electronic clinical quality measures [1] and dashboards [2,3]. However, these organizations lack evidence-based communication strategies for implementing quality measurements to work to improve their performance [4,5]. The most common approach is audit and feedback (A&F), the delivery of clinical performance summaries to providers, which demonstrates the potential for large effects on clinical practice [6-8]. However, A&F too often produces negligible effects [5,9], creating little more than distraction for providers who are fatigued by information chaos [9-11].

As currently implemented, A&F is a blunt *one size fits most* intervention. Each provider in a care setting typically receives identical metrics in a common format despite the growing recognition that *precisionizing* interventions hold significant promise in improving their impact [12-15]. A precision approach to A&F prioritizes *display of information for the single metric* that, for each recipient, carries the highest value for performance improvement, such as when the metric's level drops below a benchmark or standard for the first time, revealing an actionable performance gap [16-19]. Furthermore, precision A&F would use an optimal message format (including framing and visual displays [20-24]), based on what is known about the recipient and their context, to improve message interpretation while reducing the recipient's cognitive burden [25-28]. Well-established psychological principles, frameworks, and theories form a feedback intervention knowledge base to achieve precision A&F [16-19,29-33].

From an informatics perspective, precision A&F requires a knowledge-based system that enables mass customization by representing knowledge that is configurable at the group and individual levels. A precision A&F service uses this knowledge as *requirements* (necessary characteristics for message acceptability) and *preferences* (the relative importance of message characteristics to the recipient) to generate messages that are more likely than a *one size fits most* report to positively influence clinical decision-making and practice. An equally important informatics challenge is enabling widespread improvement through a service for precision A&F at scale. A *scalable precision A&F service* must function as an infrastructure compatible with a wide range of computing environments and supporting a wide range of clinical domains.

We developed and tested a prototype knowledge-based system for precision A&F in anesthesia care. Preliminary data show that provider preferences are not uniform, suggesting that a platform for computable knowledge is necessary to support scalable precision A&F. The Knowledge Grid platform, developed at the University of Michigan, has been shown to support *precisionizing* for clinical decision support (CDS) systems [34-36]. On the basis of our prior work, the proposed project will advance the creation of more general services for precision A&F by applying the service in anesthesia care as a demonstration domain.

Objectives

Three aims will direct this research. Our first aim is to systematically capture recipient requirements and preferences for precision A&F messages. We will identify requirements via human-centered design [37] with a provider sample from a national anesthesia quality improvement consortium of >50 hospitals and >5000 providers who receive a monthly *one size fits most* A&F email [38]. A web-based survey will elicit individual provider A&F email preferences through pairwise comparison [39]. A cluster analysis [40] of preference data will be used to identify group preferences. Our guiding research question for this aim is as follows: What differences exist in the requirements and preferences for A&F messages in anesthesia care?

Our second aim is to implement and assess a demonstration service for scalable precision A&F. We will enhance the interoperability of our system by adopting Knowledge Grid's scalable and extensible approach based on digital knowledge objects [41] and common web service application programming interface (API) technology. We will integrate our service to add an individualized message to the existing *one size fits most* A&F email sent monthly to >5000 providers. We will evaluate the performance of the precision A&F service using existing quality measurement data from >50 hospitals and conduct usability testing [42,43] with a diverse sample of providers and hospitals.

Our third aim is to assess the effects of a precision A&F service on care quality and intervention engagement. We will conduct an embedded, pragmatic cluster randomized trial of precision A&F–enhanced email versus a standard *one size fits most* A&F email to anesthesia providers. We hypothesize that providers receiving precision A&F will increase (1) care quality for improvable measures and (2) email engagement (click-through and dashboard login rates) when compared with providers receiving standard A&F emails. We will assess unintended consequences in a mixed methods process evaluation [44,45].

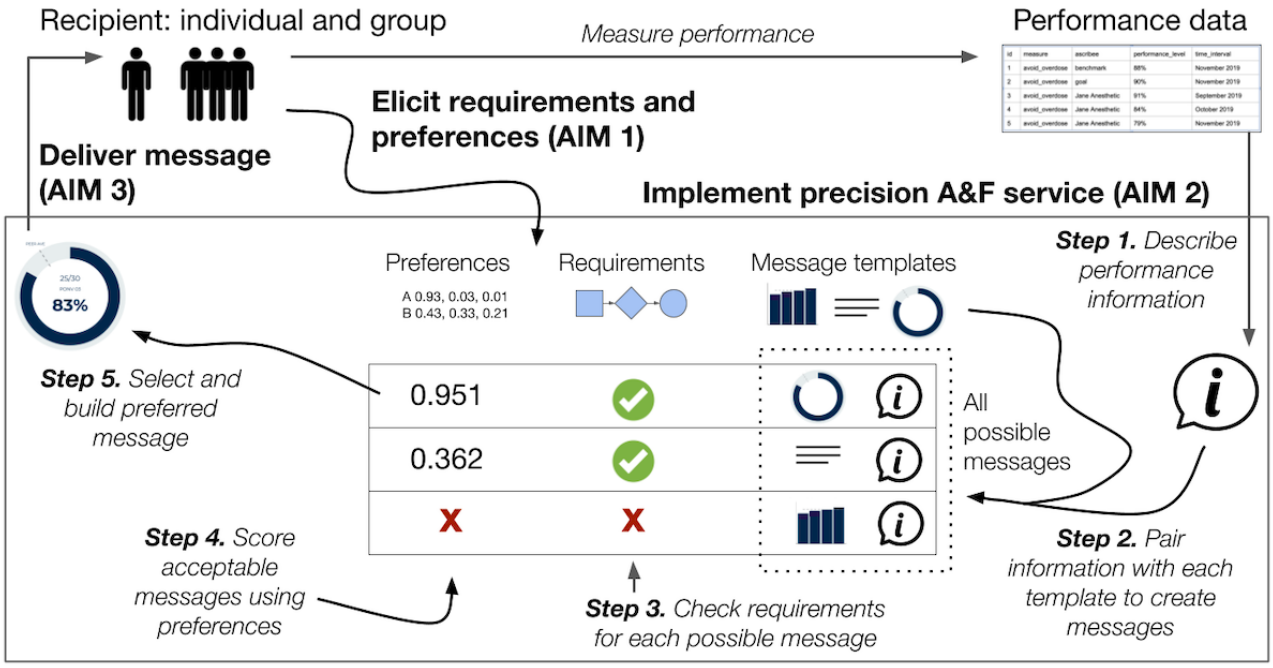
We aim to demonstrate the mass customization of A&F to improve care quality at a large scale. Following the National Institutes of Health (NIH) National Library of Medicine's vision of data *to knowledge* using a *digital objects approach* for computable knowledge, we will create potential for system-level learning about A&F to improve care quality.

Methods

Overview

We propose to achieve our aims by conducting 3 studies (Figure 1). Aim 1 is a requirements analysis and preferences elicitation study. Aim 2 is a software service development and implementation study. Aim 3 is a cluster randomized controlled trial of a precision A&F service with a concurrent process evaluation.

Figure 1. A precision feedback service. A&F: audit and feedback.

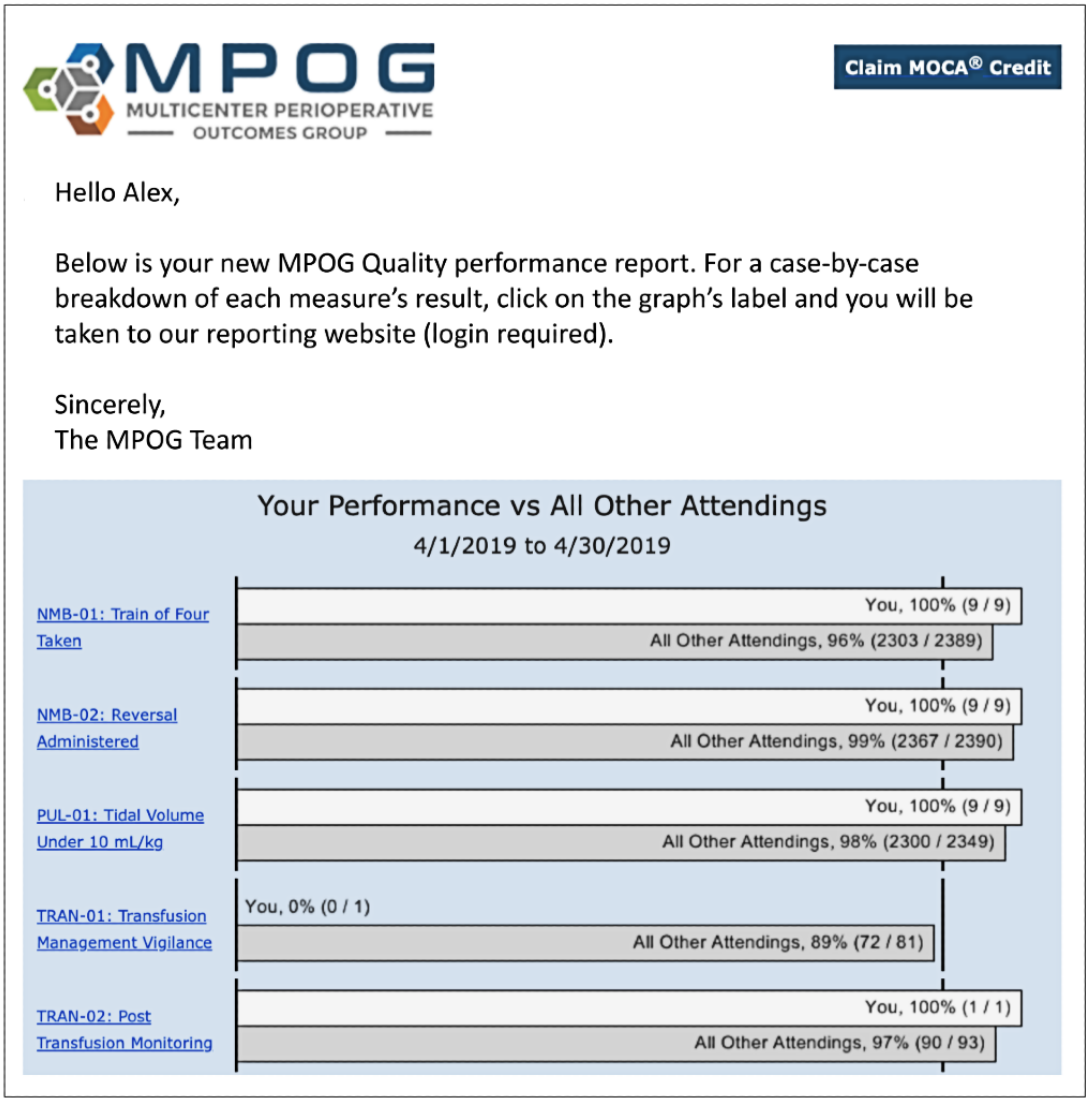


Ethics Approval

The proposed studies were approved by the University of Michigan Medical School Institutional Review Board as an umbrella project (IRBMED #HUM00194224) and for Aim 1 studies as exempt (IRBMED #HUM00204206).

This study will be conducted with the Multicenter Perioperative Outcomes Group (MPOG), a national anesthesia quality improvement consortium with >60 member hospitals in >20 states [38]. MPOG is housed at the University of Michigan and maintains a quality improvement infrastructure that represents a large-scale platform for research in precision feedback, reaching approximately 6000 anesthesia providers in monthly A&F emails. MPOG providers include certified registered nurse anesthetists, anesthesiologist attendings, and resident physicians. MPOG provider feedback emails are delivered with approximately 4 to 20 quality measures per provider, assessed, and attributed to the individual provider's care quality and clinical outcomes each month. Measures are presented either as the rate of operative case success (for process measures) or as the rate of flagged or failed cases (for outcome measures, also called inverse measures), using criteria developed and maintained for quality improvement use in the MPOG consortium [46]. Currently, MPOG sends these data in a monthly automated (*standard*) A&F email that displays all measures attributed to the recipient in a bar chart, with each measure showing bars comparing provider performance to the MPOG average for that measure (Figure 2). Process measures have a 90% goal, and outcome (inverse) measures have lower, measure-specific goals, against which the provider and their institutional peer average performance can be compared. The email directs recipients to a clinical quality dashboard also maintained by MPOG, within which providers can review their patients' case-level data to identify opportunities for improvement.

Figure 2. An example provider feedback email from the Multicenter Perioperative Outcomes Group (MPOG) setting.



Aim 1: Systematically Capture Recipient Requirements and Preferences for Precision A&F Messages

At a large scale, the usability of digital interventions becomes critical for their success [47]. Usability of precision A&F requires the elicitation of a sample of recipients' requirements and preferences at the group and individual levels. We propose to achieve usable precision feedback interventions with complementary customization strategies (Table 1).

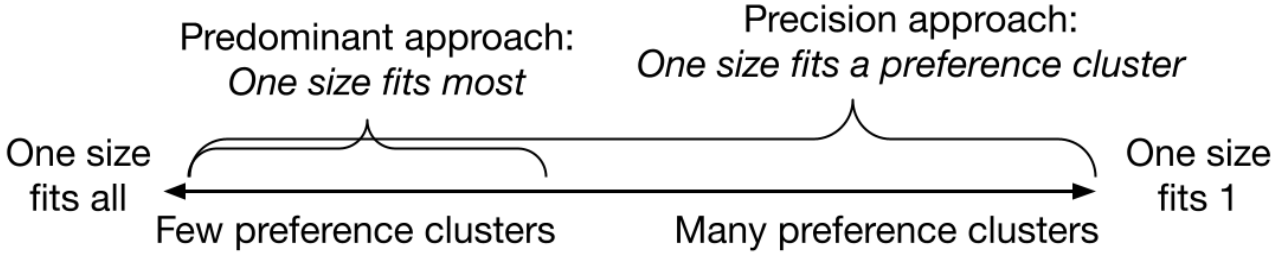
We use a novel approach comprising three customization strategies simultaneously, based on knowledge availability: (1) theory-based customization using the characteristics of an individual's performance data, (2) group-level segmentation and targeting based on requirements and preference clusters (Figure 3) obtained via human-centered design activities and cluster analysis of preference data, and (3) full tailoring using individual-level requirements and preferences obtained through user configuration of requirements and participation in a conjoint analysis survey (Table 1). This approach enables a precision A&F service to provide communication that is robust to missing knowledge at the individual or group level.

We will identify requirements via human-centered design methods [37,48] with a sample of providers who participate in the MPOG monthly provider email feedback program, receiving a standard, *one size fits most* A&F email [38]. A web-based survey will be used to elicit individual provider A&F email preferences via a pairwise comparison approach [39]. A cluster analysis [49] of individual preference data will be used to identify group preferences (Table 1).

Table 1. Precision audit and feedback knowledge for intervention success.

Knowledge class and intervention knowledge	Causal pathway component	Knowledge acquisition method	Customization strategy	Precedence
Theory				
Requirements	Preconditions	Representation of psychological theories and frameworks	Theory-driven customization	Low
Preferences	Moderators	Representation of psychological theories and frameworks	Theory-driven customization	Low
Group				
Requirements	Preconditions	Human-centered design	Targeting and segmentation	Medium
Preferences	Moderators	Cluster analysis of conjoint analysis data	Targeting and segmentation	Medium
Individual				
Requirements	Preconditions	Provider configuration of settings	Tailoring and individualization	High
Preferences	Moderators	Conjoint analysis survey	Tailoring and individualization	High

Figure 3. A one size fits *n* spectrum.



Our guiding research question for this aim is as follows: "What differences exist in provider requirements and preferences for A&F messages in anesthesia care?" We will identify and describe these differences in terms of the message information and format [50], based on 2 application ontologies we developed for this purpose using Basic Formal Ontology [51] as an upper-level ontology. The Performance Summary Display Ontology (PSDO) [52] describes information and formatting elements of performance summaries. In a preliminary evaluation of PSDO, we successfully described published examples of feedback reports and dashboards from a wide range of clinical settings [50]. The Causal Pathway Ontology describes influence pathway components, including mechanisms, preconditions, moderators, and outcomes (Figure 4), based on a causal pathway modeling approach [53].

When used together, PSDO and the Causal Pathway Ontology provide a well-defined domain for reasoning about performance summaries within feedback messages and their anticipated effects.

To develop group-level requirements, we will interview a sample of approximately 50 providers from up to 25 MPOG member hospitals to collect qualitative data on precision feedback requirements. We will ask participants to *think aloud* while they read prototype precision feedback messages to observe their cognitive processing of the precision feedback prototypes (Figure 5). We will analyze the interview data using template analysis, in which 2 researchers will use a codebook we developed for this purpose. New themes will be developed as requirements in the form of user stories during the analysis phase [37]. After coding is complete, requirements will be coded with classes from our ontologies and from the Behavior Change Intervention Ontology [54] to develop computable user stories at the group level.

To elicit preferences, we will conduct a web-based survey using a pairwise comparison method with an adaptive conjoint analysis. Adaptive conjoint analysis is a marketing research method [55,56] increasingly used to elicit patient preferences in health care [57] and has been used to identify *preference phenotypes* [58,59]. Preferences can be represented quantitatively as utilities that indicate the relative importance of specific attributes and levels (ie, part-worth utilities) of a product or service. These preference models can be used to represent the relative importance of message characteristics specified in PSDO based on their role as preconditions for feedback intervention success. We developed a web-based survey using 1000Minds software (1000Minds Ltd) [60], which presents participants with pairwise comparisons of message characteristics in 3 dimensions of preconditions (comparator, feedback sign, and trend) and 1 dimension for the visual display type. We will recruit MPOG providers from diverse hospitals and geographic regions, and with diverse demographics, to participate in the study and to complete the 10-minute survey. We estimate that recruiting approximately 300 participants is feasible based on a 10% response rate observed in our previous recruitment in this population.

Figure 4. A causal pathway model for precision audit and feedback (A&F) interventions.

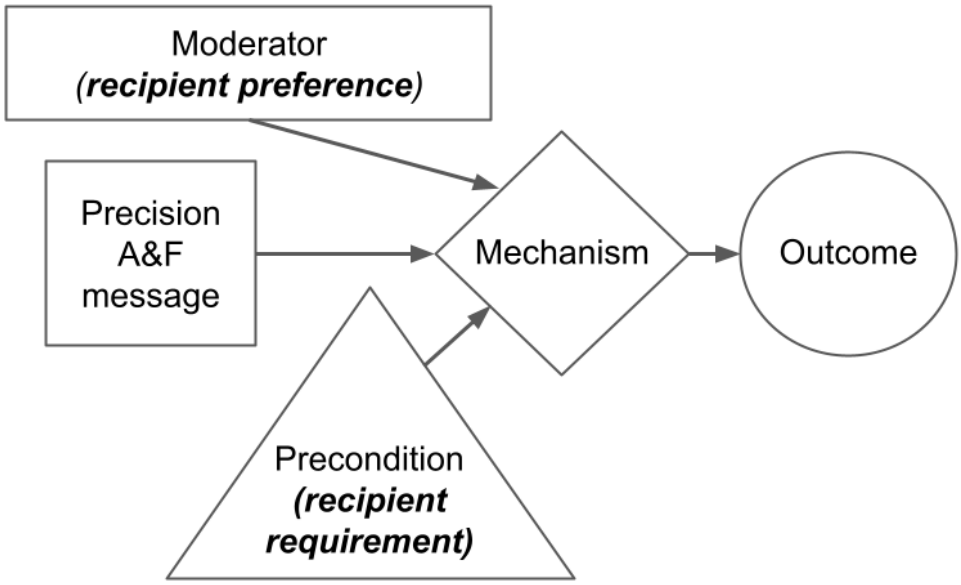
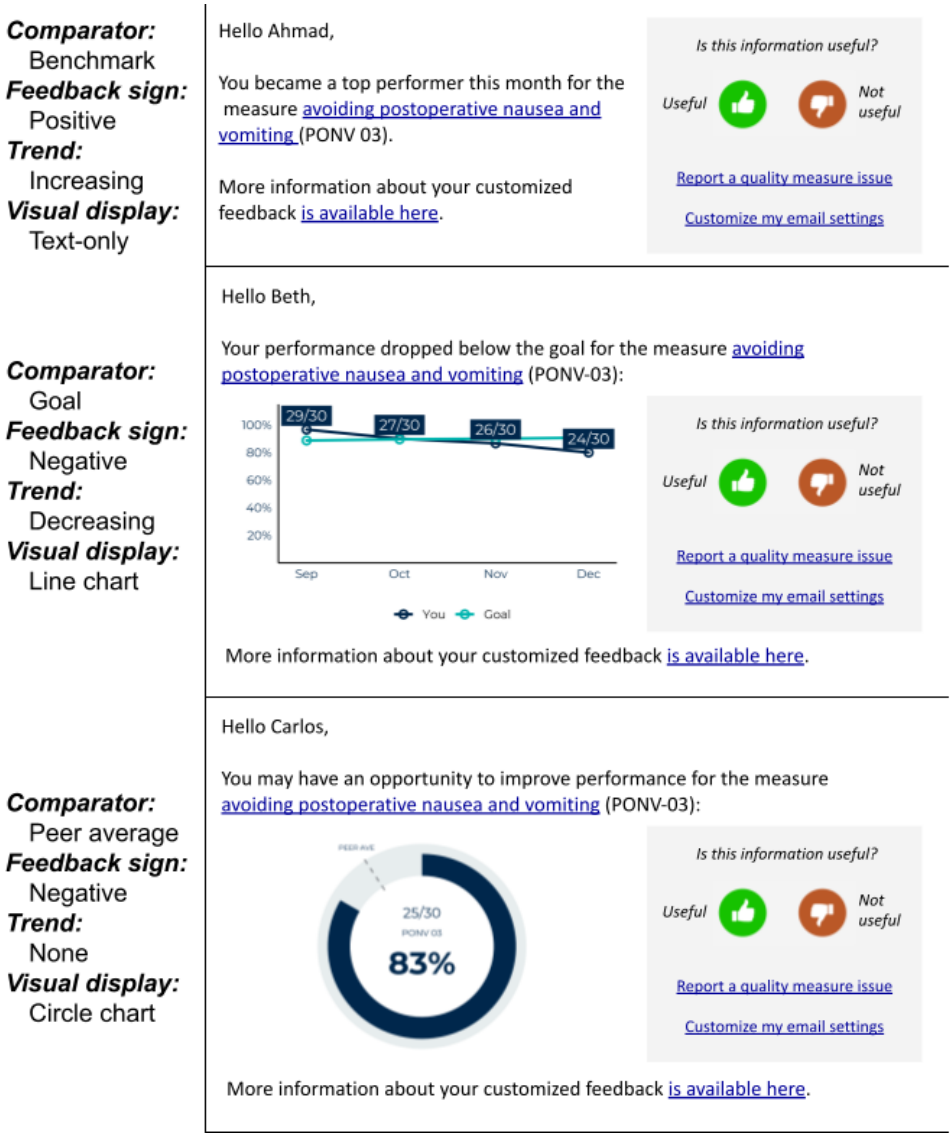


Figure 5. Prototype precision feedback email messages.



The web-based survey data will be used to produce individual-level preference models via an adaptive conjoint analysis of provider preferences for precision feedback emails. 1000Minds uses a method called Potentially All Pairwise RanKings of all possible Alternatives that allows reduction of the total number of comparisons to be made through assumed transitivity of preference and that permits participants to indicate indifference toward the 2 choices to be compared [39]. This approach also uses repeated questions to check the consistency of preferences as a test of the assumption of transitivity for each participant. This analysis will produce part-worth utilities, also called preference weights, that can be averaged across all participants to establish group mean weights.

Individual rankings for all attributes from the adaptive conjoint analysis can be used for a cluster analysis to identify groups of participants with similarities across one or more preference characteristics. We will conduct a hierarchical cluster analysis [40] of preference data using participant characteristics to identify group-level preferences of population segments for the targeting and segmentation strategy of the precision A&F service (Table 1). We will use the NBClust [61] package in R (R Foundation for Statistical Computing) [62] to identify the optimal number of clusters for our data.

There are potential problems that may require alternative approaches to enable our successful completion of this aim. Self-selection bias in recruitment could reduce participant representativeness of the provider population. To prevent this issue, we will actively recruit providers who do not hold the position of the MPOG QI Champion and who do not routinely use the dashboard, which we estimate to be a large proportion of the population. On the basis of our preliminary studies, we anticipate a significant variation in preferences. In the unlikely event that preferences for feedback emails are highly similar across all dimensions of all message characteristics (including comparator, feedback sign, trend presence, and visual display), the diversity of providers' individual performance levels will nevertheless enable precision A&F messages to be individually prioritized using theoretical requirements and preferences.

Using utilities to represent provider preferences imposes several assumptions that may not hold: provider preferences may not be complete, may not be linear in probability, and may not be stable over time. The collected data will enable us to learn about the validity of these assumptions. We will test for consistency and stability of preferences by conducting 2 rounds of the adaptive conjoint analysis (years 1 and 3) to observe preference changes. We will also consider (1) diversity of participants along demographics and professional roles, (2) representativeness of the provider population, and (3) diversity of organizations and clinical settings (community hospitals and academic medical centers) from which participants are recruited, and strive to maximize these and other forms of diversity and representativeness. We will strive to recruit participants from a representative gender mix within the anesthesia provider population.

Aim 2: Implement and Assess a Demonstration Service for Scalable Precision A&F

We will make our knowledge-based system interoperable by conforming to open standards in a scalable and extensible service model. We will do this by developing a small collection of modular digital knowledge objects [41] that can each be shared and managed independently and a corresponding modularized web service API approach. Next, we will move from a *one size fits most* A&F email message sent to >6000 anesthesia providers each month to test the processing of data for mass-customizing message content computed by and coming from the precision A&F service. We will then test service performance in terms of data processing capability using existing quality measurement data from a subset of the available 60 hospitals and conduct usability testing [42,43] to assess feasibility. Our research goal for this aim is for the service to become operational and pass performance benchmarks for system functioning at a national scale, processing data for at least 30 hospitals in at least two separate regions of the United States, but not yet sending precision feedback messages at this step.

Precision A&F may have a large impact when it can be easily deployed and managed as a scalable A&F web service by quality improvement organizations that serve many providers. Demonstrating success at a large scale requires a technical platform that enables mass customization of computable knowledge capabilities provided by the Knowledge Grid platform. This system development and implementation study is consistent with the NIH National Library of Medicine's vision of a computable knowledge approach using digital objects that can be maintained and curated in accordance with the FAIR (Finable, Accessible, Interoperable, and Reusable) principles [63].

We will package our precision A&F specifications and algorithms in digital knowledge objects for each type of recipient knowledge (Table 1) and for the major components of the precision feedback system (Figure 1). This packaging step is to establish the easily deployable and shareable precision A&F service, built on Knowledge Grid technology and processes, including the following: packaging and deploying knowledge objects, standing up knowledge object–backed service APIs using OpenAPI standard web service specifications, creating a deployment specification to facilitate deployment into existing information technology environments, conducting precision A&F web service testing, including unit and integration testing, and finally implementing the ready-to-use service.

The implemented precision A&F service will routinely and automatically apply requirement and preference knowledge about recipients in a just-in-time approach based on a specified order of application and precedence (Table 1). Given that many recipients are not expected to provide individual-level requirements or preferences, we will at a minimum use theory-based requirements knowledge for precision A&F for all recipients. Before each monthly feedback cycle, we will reapply new requirements or preference knowledge as part of an automated and routine system adaptation process for all participants. Group requirements and group mean preferences

will be automatically assigned based on computable user stories and weighted means, respectively, for the recipients' professional role and site data. Cluster-based preferences will be automatically assigned based on the detection of a significant statistical association (eg, using multinomial logistic regression) between recipient characteristics and a preference cluster. Individual recipients will be routinely offered the opportunity to provide requirements via a precision A&F dashboard–based configuration page and to provide preference data via the web-based survey developed in Aim 1. Individual requirements and preferences will take the highest precedence, and will be used to overwrite any automatically assigned group or theory-based preferences (Table 1).

To test the function of the system, we will generate synthetic requirements and preference data and collect existing MPOG performance data for analysis. We will test the performance of the service for the processing of email-based precision A&F for approximately 6000 anesthesia providers but will not yet send any messages generated at this step. We will optimize system functions to minimize production time and computation costs within a monthly reporting cycle.

We will implement the service within MPOG's provider email program, such that providers at any institution selected for piloting can receive precision A&F messages for testing purposes. We will recruit a sample of up to 50 providers from 4 institutions, including 2 community hospitals and 2 academic medical centers. We will invite participants to use the web-based survey to generate individual preference data and to configure their individual precision A&F email requirements. We will conduct *live usability testing* [43] by scheduling video calls to conduct a think-aloud testing of a sample of emails received with providers' current performance information. We will assess the collection of email engagement data using click-through data for email links.

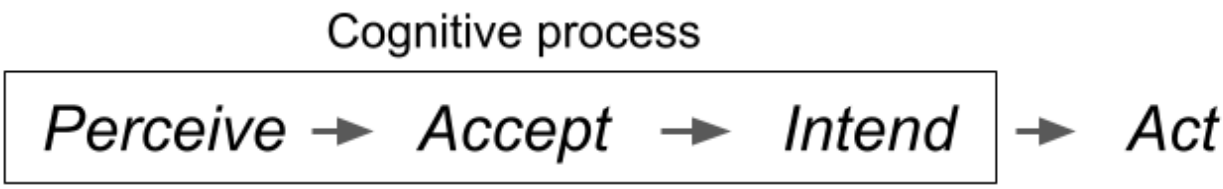
As the Knowledge Grid technology and the common standards it uses have already been demonstrated to function as needed for our purposes, we do not anticipate significant technical barriers to achieving this aim. A possible problem is unanticipated complexity resulting from diverse requirements, organizational culture, and ecosystem changes, as requirements are specified for precision feedback. To address this problem, if significant, we will reduce the scope of the demonstration system in terms of the number of performance measures to be maintained and will implement the system within a reduced number of participating hospitals that have a larger proportion of providers before expansion throughout the consortium. This aim will be successfully completed when the precision A&F service becomes operational at its sites of implementation using the Knowledge Grid platform technology and can pass performance benchmarks for system functioning at a national scale, processing data for at least 30 hospitals in at least two separate regions of the United States.

We will use the following software development strategies to ensure a robust and unbiased approach: (1) use open standards that are broadly adopted for knowledge representation, software development, and metadata management and (2) develop open-source software in a public repository (GitHub) from the start (open development process) under an open-source license. Throughout this process, we will also ensure a robust and unbiased approach by eliciting our values as a project team and reviewing the organization's values to seek agreement on our fundamental goals. Furthermore, we will consider the diversity of our team members to strive to reduce bias through diversity and inclusion practices, such as sending position openings to communities and organizations with team members who may be underrepresented in our team and department. Furthermore, we will consider the diversity of participants, including gender, in interviews and seek opportunities to involve participants in decision-making for the design of the system.

Aim 3: Assess the Effects of a Precision A&F Service on Care Quality and Email Engagement

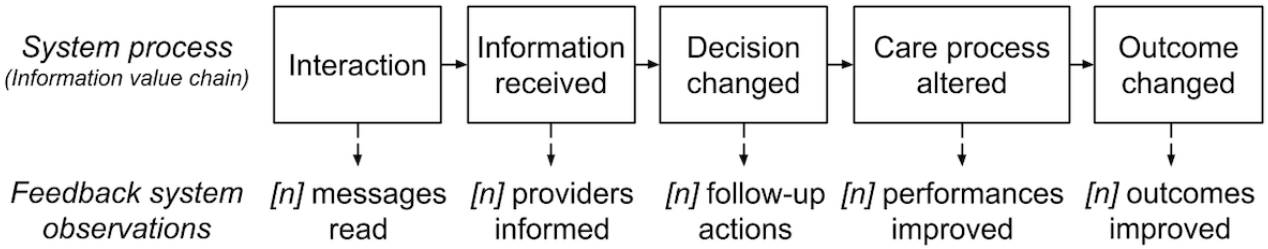
Behavior change theories offer many potential explanations of what works when using feedback interventions to influence human behavior [64-67], and the formalization of these theories is ongoing [68]. Successive efforts have aligned key theories [29,30,69] around a sequence of cognitive steps that occurs between the perception of feedback and action taken in response, resulting in a common sequence of constructs that represent necessary steps for feedback intervention success [17-19,29,30] (Figure 6).

Figure 6. A process model for feedback intervention success.



Information value chain theory [70], a theory developed for the purpose of assessing technology success, presents a strikingly similar sequence of steps and has been applied to A&F to support recognition of several points of failure along an information value chain [44,45,70]. For example, when feedback is delivered via email, not all providers will open and read every email. Of those who read the email, not all decide to follow up on the information (Figure 7). A value chain analysis can reveal how a high proportion of information in A&F reports may lack value from the outset and reduce the likelihood of ongoing provider engagement with the intervention. When each step in the chain can be associated with an observable event via email link tracking and log file analysis, an information value chain approach offers an unobtrusive, theory-based evaluation approach for A&F [71] with high potential to reveal how feedback interventions are made more effective.

Figure 7. An information value chain for feedback intervention success.



We will conduct an embedded cluster randomized trial of precision A&F–enhanced email versus a standard A&F email to anesthesia providers. We hypothesize that providers receiving precision A&F will increase (1) care quality for improvable measures and (2) email engagement (click-through and dashboard login rates) when compared with providers receiving standard A&F emails. We will also assess unintended consequences in a mixed methods process evaluation [44,45].

The selected outcomes for the trial are consistent with information value chain theory [45], reflecting the influence of information received on decision-making and behavioral response in terms of observable actions. For example, an observable response action indicating *decision changed* success is clicking on a link inside the enhanced or standard A&F email; performance on improvable process measures reflects *care process altered* success and performance on outcome measures reflects *outcome changed* success. Email engagement rates are used to support the retrospective calculation of event probabilities that can be associated with the characteristics of the recipient, group, and email message.

To understand the potential impact of precision A&F, we will implement and study the effects of a demonstration system at a large scale, supporting the implementation and maintenance of computable knowledge about feedback recipients' requirements and preferences in a wide range of settings. As there is a potential for software-associated unintended adverse consequences [11], we will conduct a mixed methods process evaluation that is concurrent with the trial to inform our understanding of the observed effects.

Our study design includes a 2-arm cluster randomized controlled trial and a mixed methods process evaluation. In this study, the intervention arm will receive an enhanced monthly email containing precision A&F, and the control arm will receive the standard *one size fits most* A&F monthly email. Secular trends and regression to the mean effects, due to selection of measures on which performance is relatively low will be balanced across the 2 arms. All data for the trial will be provided by MPOG via its quality measurement data collection and analysis infrastructure, which is housed at the University of Michigan. The primary outcome will be the average postintervention performance level (*P*) for improvable measures (subscript *m*), where

$$P_m = 100 \times (\text{number of operative case successes})_m / (\text{total number of operative cases})_m \textbf{(1)}$$

Each participant's performance level on each measure will thus vary from 0 to 100. Scores on some MPOG measures are historically and consistently high, creating the potential for ceiling effects. The improvable measures are defined as clinical process measures with a mean score historically <98% for all providers participating in the MPOG provider feedback email program. For the proposed study, we will determine the set of improvable measures using up-to-date performance data. On the basis of the current performance data from all MPOG providers, 7 improvable measures may be included. The following are three examples:

- BP-02: Avoiding Monitoring Gaps. Percentage of cases where gaps >10 minutes in blood pressure monitoring are avoided.
- NMB-01: Train of Four Taken. Percentage of cases with a documented Train of Four after the last dose of a nondepolarizing neuromuscular blocker.
- PUL-02: Protective Tidal Volume, 8 mL/kg predicted body weight. Percentage of cases with median tidal volumes ≤8 mL/kg.

Secondary outcomes will be average rates of email engagement in the postintervention period, including email click-through rate (CTR) and dashboard login rate (L), where

$$CTR = 100 \times (\text{number of recipient's emails with a clicked link}) / (\text{total number of emails}) \textbf{(2)}$$

$$L = 100 \times (\text{number of months with an email recipient's dashboard login event}) / (\text{total number of months}) \textbf{(3)}$$

Each participant's CTR and dashboard login rate will vary from 0 to 100. Email CTR is an essential measure for advertising systems that is widely used in email marketing studies. CTR will be measured using link tracking with unique URLs for each email link in the precision A&F and standard A&F emails. Dashboard logins will be measured using log file analysis. The MPOG-wide dashboard login rate is estimated to be low, with approximately 6% of MPOG providers logging in each month.

Predictor variables will include discrete and continuous measures. Discrete variables will include the recipient's (1) study arm (*precision-enhanced messages*, *standard messages)*, (2) hospital type *(community, academic medical center)*, and (3) professional role (*certified registered nurse anesthetist*, *resident*, *attending*). Continuous variables will include (1) average preintervention performance level (for improvable measures, calculated in the same way as postintervention performance) and (2) total number of months since the first month of participation in MPOG.

MPOG has >60 hospitals and a population of >6000 providers; however, because of the potential for hospital-level factors limiting participation, such as electronic health record

implementation or reorganization activities, we estimate that at least 30 hospitals will be included. We will exclude providers who (1) end participation in the MPOG provider feedback email program for any reason, (2) change institutions, or (3) change professional roles (eg, transition from resident to attending) before the end of the intervention period. After exclusion of individual providers, we anticipate that we will engage approximately 3500 providers.

We will collect 1 year of retrospective performance and email engagement data at participating hospitals during the preintervention period. We will randomize hospitals to be in either arm of the study by using a restricted randomization approach to minimize baseline imbalance [72]. All providers participating in the MPOG email program at intervention sites will begin receiving precision A&F–enhanced emails at the start of the intervention period. Providers in the control sites will continue to receive the standard monthly A&F email. All providers at all participating hospitals will be notified of the study and offered the option not to participate. We expect few *opt-outs* as all providers in the sample are established MPOG participants, and the study will not intrude on their time.

To analyze the primary and secondary outcomes, we will use two-level (hospital and individual) hierarchical linear modeling. We will account for clustering and report the intraclass correlation coefficients. In this statistical model, the primary hypothesis for this study is explored through a main effect by study arm (precision-enhanced messages vs standard messages). This study has a large population of providers (estimated 1750 per study arm) across 30 hospitals. In exploring our primary hypothesis, we will test for differences in improvable measure performance across the 2 treatment groups at the individual provider level. The sample size will allow us to detect small differences across the study arms. On the basis of the most recent available MPOG data, the SD of performance at the individual level, averaged across 7 improvable performance measures, was 23 scale points. From this, we determined that our sample size has 80% power at 2-tailed α=.05 to detect a difference of 2.2 scale points across the 2 study arms (Cohen d=0.096).

We will conduct a process evaluation to understand the context, implementation process, and mechanisms associated with the precision A&F service during the trial period. We will conduct quantitative and qualitative methods in alignment with a process evaluation framework for complex interventions [73]. In the quantitative evaluation, we will monitor events in the information value chain and calculate event probabilities for email open rates, follow-up decisions, and performance improvements in processes and outcomes. We will analyze relationships between message characteristics and event likelihood and calculate the expected utility of messages using utility and likelihood. We will analyze feedback from email message usability questionnaires and responses to answer the following questions:

1. What proportion of each step in the information value chain was achieved?
2. What information was correlated with higher completion of steps in the information value chain?
3. What message formatting was correlated with higher completion of steps in the value chain?
4. What mechanisms, preconditions, and moderators were correlated with higher completion of the information value chain?

We will conduct a qualitative process evaluation to understand perceptions of the precision feedback and unanticipated adverse effects of the intervention. We will conduct qualitative phone or video call interviews with stakeholders and providers from 3 to 5 sites. We will thematically analyze the effects of the intervention using the Tailored Implementation of Chronic Disease framework in a template-editing approach. We will also aim to identify the mechanisms of action reported by participants. The qualitative process evaluation will aim to answer the following questions:

1. What potential differences in the intervention effect may be due to sex or gender and race or ethnicity?
2. What theoretical mechanisms of action appear to have been used for precision A&F emails?
3. To what extent might unintended adverse consequences of precision A&F have occurred?
4. What differences exist in provider receptiveness to precision feedback emails, in association with recipient, group, or message characteristics?

As a digital intervention, standardization for study participation and adherence to the study protocol are mostly infrastructural issues that have been addressed by MPOG in its establishment of A&F. We expect that the automation of feedback delivery will therefore benefit from a high level of standardization and adherence. However, we also will use our secondary outcomes of email engagement to support quality assurance. We will develop measures for the quality of the intervention and monitor their performance to identify software-based issues with the planned delivery of precision feedback.

For the trial, all data collected are part of the routine monthly data collected by the MPOG consortium, which has established a mature infrastructure that includes standardization, monitoring, and quality assurance processes. We will extend the existing MPOG infrastructure to conduct the trial, leveraging an extensive body of existing resources and infrastructure for routine A&F. Data management and quality control for the study will be managed by the MPOG team that routinely manages and analyzes performance data. We will develop software-based statistical analysis for quality control of the study data to estimate the effect of the interventions and to support monitoring of the intervention effect before the end of the trial. We have planned for a 6-month period to allow for adequate time to complete data analysis following the trial. We anticipate that the quantitative analysis can be completed within weeks of the conclusion of the trial and that the bulk of the 6-month period will allow time to complete a qualitative process evaluation of the trial, which will be ongoing and concurrent with the randomized controlled trial.

A foreseeable problem for the trial is that performance is high overall, which reduces the potential impact of precision feedback on performance. Our process evaluation will enable us to observe reactions to positive feedback and understand the

benefits to providers. In the event that providers habituate to messages at higher-than-anticipated rates during pilot implementation (Aim 2), we will develop and test requirements for message novelty. By using restricted randomization to minimize baseline imbalance [72], we will ensure that hospitals are allocated equitably and minimize the risk of bias. We will analyze the gender balance in participation and consider gender as a key factor in our process evaluation.

Results

The proposal was funded in September 2021 with a 4-year timeline. Work on the technical integration of the precision feedback software with the MPOG email system began in January 2022. Data collection for Aim 1 began in March 2022, with 3 participants recruited at the time of manuscript submission. We plan for a 24-month trial timeline, with the intervention period of the trial beginning in March 2024.

Discussion

Hypothesis

Our primary hypothesis is that providers who receive precision A&F will increase care quality for improvable measures more than those who receive standard A&F emails. We also anticipate that engagement, in terms of email CTR and dashboard login rate, will be greater among providers receiving precision A&F.

Comparison With Previous Work

The effects of A&F are mixed (median 4.3% absolute improvement, IQR 0.5%-16%) [7], indicating great uncertainty regarding how and when A&F works. Although this lack of knowledge has persisted for decades [5,74], A&F is increasingly being implemented electronically at a larger scale in clinical quality dashboards [2,3]. Furthermore, ongoing efforts to standardize and automate care quality measurement [1] further increase the potential volume of data for A&F. Without gaining knowledge about how and when A&F is effective, this inefficiency and the lost opportunities to improve care are likely to increase.

Best practice guidance about designing A&F offers methods for satisfying *most* providers' requirements and preferences in a population to produce A&F that is usable and useful [48,75,76]. However, as an intervention scales up, its usability becomes increasingly important owing to the greater cost in time and attention across more diverse contexts [47]. Improving the usability of A&F requires recognition of multiple dimensions of *fit* for A&F, including the formatting of the message, the success of which depends on the characteristics of the message recipient, their context, and the visual representation itself [21,50,77,78]. Efforts to recognize this diversity have motivated our work to develop and study precision feedback interventions, which hold significant promise for improving the impact of digital interventions [12-15].

Understandably, efforts to improve A&F have focused on delivering actionable information to providers, which may be an important effect modifier of feedback interventions [6,29]. However, this focus can translate to the prioritization of negative feedback and social comparison that can demotivate providers [32,69,79]. For example, when a provider is learning a new skill, comparison with peers that show negative feedback can convince providers to abandon the skill-learning task [17,79]. Focusing solely on actionability results in a myopic view of the power of feedback interventions [80]. A broader view enables feedback interventions to leverage the motivation that arises from the recognition of achievements [31,33,69,81,82], even when performance is high, which can motivate increased effort, continuing learning, and goal setting [17].

CDS offers an extensive body of knowledge that could inform the study of A&F, exemplified by the CDS Five Rights framework [83] (right person, right information, right intervention format, right channel, and right timing in workflow); however, to our knowledge, this intersection of ideas remains largely unexplored [84]. A key issue that has prevented the application of CDS knowledge to A&F is a lack of well-defined terms and concepts used in A&F that hinder the ability of meta-analyses to recognize equivalent constructs for Five Rights. Efforts to standardize these elements [50,85] have yet to be broadly established. We developed an ontology of performance information in A&F reports, PSDO, and evaluated a sample of published reports [50], representing early progress toward this goal. Furthermore, a known problem with most CDS developed to date is that the causal mechanisms that CDS designers expect to drive improvement are not made explicit or even well understood [86]. Our approach to mass customization of A&F leverages causal mechanisms made explicit in our feedback intervention knowledge base that may benefit our understanding of its influence.

To our knowledge, this study will use for the first time an integrated representation of recipient requirements and preferences using theoretical constructs that direct the production of precision A&F messages. Using causal pathway models [53] (Figure 4) to model requirements and preferences as preconditions and moderators that affect intervention success, we gain the capability to prioritize messages based on theoretical mechanisms [17-19,29,32,87] and visual communication factors [21,27,77,78,88] together with what is known about the message recipient.

The proposed aims will collectively demonstrate a precision feedback service developed using an open-source technical infrastructure for computable knowledge management. We envision this approach to conform to the NIH National Library of Medicine's vision of *data to knowledge* by demonstrating precision feedback using a *digital objects approach* [89,90]. By implementing and evaluating a demonstration system for precision feedback, we create the potential to observe the conditions under which feedback interventions are effective.

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Conflicts of Interest

ZLL has received research support, paid to the University of Michigan and related to this work, from the National Library of Medicine (K01 LM012528). AJ has received research support, paid to the University of Michigan and unrelated to this work, from Becton, Dickinson and Company. NS has received research support, paid to University of Michigan and unrelated to this work, from Merck & Co. NS received support, paid to the University of Michigan, for his role as Program Director of Anesthesiology Performance Improvement and Reporting Exchange (ASPIRE) Collaborative Quality Initiative, and has received research support from Edwards Lifesciences, Apple Inc, and National Institute on Aging (R01 AG059607), paid to the University of Michigan and unrelated to this work.

Multimedia Appendix 1
Peer-review report by the Biomedical Informatics, Library and Data Sciences Review Committee (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 89 KB - resprot_v11i5e34990_app1.pdf]

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Abbreviations

A&F: audit and feedback
API: application programming interface
CDS: clinical decision support
CTR: click-through rate
FAIR: Finable, Accessible, Interoperable, and Reusable
MPOG: Multicenter Perioperative Outcomes Group
NIH: National Institutes of Health
PSDO: Performance Summary Display Ontology

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Protocol

A Parent-Based Intervention for Reducing High-risk Social Media Cognitions, Alcohol Use, and Negative Consequences Among Adolescents: Protocol for a Randomized Controlled Pilot Study

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Abstract

Background: The prevalence of adolescent alcohol use continues to be a public health concern. Although adolescents spend an increasing amount of time with their friends, parents remain an important source of support and continue to play a key role in the lives of their adolescents. Extensive research in this area has resulted in parent-based intervention (PBI) efforts to prevent or reduce adolescent alcohol use. However, one major limitation of PBIs is that they do not currently consider the large role that social media plays in adolescents' lives and in relation to their alcohol use. We will add to the literature by developing and refining a web-based PBI designed to reduce both high-risk social media cognitions and alcohol use among adolescents.

Objective: The central goal of the proposed study is to develop, refine, and pilot a web-based PBI to reduce both high-risk social media cognitions and alcohol use among adolescents.

Methods: A total of 100 parent-teen dyads will be randomly assigned to one of the following 2 conditions: intervention or control. Parents in the intervention group will be given access to the web-based PBI and suggestions for working through the PBI modules with their teens. The parent-teen dyads will fill out 3 questionnaires: a baseline questionnaire, 1-month questionnaire, and 6-month questionnaire.

Results: Recruitment and enrollment will begin in August 2022. Upon completion of the intervention trial, we will examine the feasibility, acceptability, and preliminary effect sizes of the newly developed web-based PBI.

Conclusions: This study has the potential to open doors for future studies examining the clinical implications of an efficacious web-based PBI to reduce alcohol use and high-risk cognitions about alcohol displays on social media.

Trial Registration: ClinicalTrials.gov NCT04333966; https://clinicaltrials.gov/ct2/show/NCT04333966

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KEYWORDS

parent-based interventions; alcohol; pilot study; social media; mobile phone

Introduction

Background

The prevalence of adolescent alcohol use continues to be a public health concern [1]. Alcohol-related problems occur in school and interpersonal, social, or health domains [2]. Almost 25% of 14- to 15-year-olds drink alcohol, with ≥90% of all alcohol consumed by adolescents being consumed in the form of heavy episodic drinking [3]. Research indicates that by 15 years of age, approximately 35% of teens have had at least one drink, and by 18 years of age, that number rises to 65% [4]. Past-year use of alcohol is reported by 17.6%, 38.3%, and 55.6% of 8th, 10th, and 12th graders, respectively [5]. Considering that alcohol is directly linked to the leading causes of death in adolescence, the US Department of Health and Human Services has listed the reduction of underage alcohol use as one of their major objectives of Healthy People 2030 [6]. This study protocol directly answers this call.

Although adolescents spend an increasing amount of time with their friends [7,8], parents remain an important source of support and continue to play a key role in the lives of their adolescents [9,10]. Extensive research in this area has resulted in parent-based intervention (PBI) efforts to prevent or reduce adolescent alcohol use [11]. Research has shown that teens whose parents received a PBI reported less alcohol use and fewer alcohol-related consequences up to a 9-month follow-up than controls [12-15]. However, one major limitation of PBIs is that they do not currently consider the large role that social media plays in adolescents' lives and in relation to their alcohol use.

Most (90%) adolescents are on social media [16], and their Facebook, Instagram, and Twitter profiles include alcohol content [17,18]. Thus, adolescents are exposed to social media alcohol displays, which are associated with high-risk cognitions and alcohol use [19-24]. Research has argued that existing parental mediation techniques grounded primarily on television and film media have fundamental inadequacies when applied to media such as websites, social media, and mobile apps, as they do not account for the interactivity, immersive web-based environments, and mediated communication innate to social media [25]. Furthermore, most PBIs are presented in a static manual form [15,26,27]. We are unaware of any study to date that has developed and tested a PBI about alcohol use and the role of social media in adolescent alcohol use. As such, we will add to the literature by developing and refining a web-based PBI designed to reduce both high-risk social media cognitions and alcohol use among adolescents.

Adolescent Alcohol Use

Research concerning the initiation and progression of adolescent alcohol use indicates that most youth initiate use by experimenting with alcohol during early adolescence and that such early experimentation can lead to later heavy alcohol use [28-33]. Early initiation of alcohol use is also associated with various additional negative outcomes in later adolescence and early adulthood such as violent and delinquent behavior, poor physical health, and mental health problems [31,32]. As this general pattern of alcohol use initiation and escalation is well documented, many prevention programs for adolescent alcohol use aim to prevent early-stage alcohol use or at least delay the initiation or onset of alcohol use among adolescents. Given how prevalent and potentially harmful adolescent alcohol use is, and the fact that studies have not indicated increased alcohol involvement following universal interventions [34,35], universal prevention of alcohol use is an appropriate choice for this age group [36].

Preventing underage alcohol use and reducing the proportion of people who engage in heavy drinking are listed as major objectives of Healthy People 2030 [6]. To address these issues, it is important to consider factors that may be related to initiation and progression of alcohol use among adolescents. Parent-teen communication familial factors have frequently been focused on in relation to adolescent development and have been shown to inform effective interventions [37]. Although adolescents usually strive to become more autonomous from their parents and spend an increasing amount of time with their friends [7,8], parents remain an important source of support and continue to play a key role in the lives of their adolescents [9,10].

A growing body of literature provides evidence for reductions in adolescent drinking associated with parental influences, including greater parental monitoring [38-40], less favorable parental attitudes and beliefs about drinking [41,42], and more positive quality of the parent-child relationship and communication [43-45]. Miller-Day and Kam [46] found that targeted parent-teen communication, defined as "direct and indirect, as well as one-time and ongoing, conversations specifically about alcohol," was associated with lower levels of adolescent drinking. In addition, Wood et al [47,48] discovered that parental communication variables were related to lowered alcohol use and related problems. These findings illustrate that parental influence is relevant to adolescent decision-making regarding alcohol use, even as their children transition from adolescence to young adulthood. As parents are likely to exert a major influence on their teens' behavior including their substance use, parents are important agents who should be included in intervention efforts.

Social Media and Adolescent Alcohol Use

Aided by the convenience and constant access provided by mobile devices, especially smartphones, research indicates that 89% of teens report going on the internet at least multiple times per day, including 45% who say they go on the internet *almost constantly*, and much of this time is spent on social media [49]. Adolescents are the age group that uses social media the most, with research showing that up to 97% of people in this age group are members of at least one social media platform. Although Facebook used to be the most commonly used social media platform among adolescent users, only a few years ago, it has rapidly declined in popularity (it is currently used by 51% of adolescents). Currently, the top 3 platforms are YouTube (used by 85%), Instagram (used by 72%), and Snapchat (used by 69%) [49]. Notably, almost 5 times as many adolescents use social media (29%) instead of email (6%) for daily communication [16], indicating that social media is a central way in which adolescents communicate with peers.

A significant number (between 20% and 30%) of adolescent social media profiles include alcohol-related content or displays, with most displays being proalcohol or favorable toward heavy alcohol use [17,18,20,23]. This indicates that adolescents are both the creators and viewers of alcohol-related content on social media platforms. Alcohol-related displays on social media have repeatedly been found to be associated with adolescent problem drinking [21,22,24,50-52]. There is a robust relationship between exposure to social media alcohol content and alcohol consumption 6 months later, which persists even after close friends' drinking is accounted for [53]. These findings indicate that alcohol references on social media do not simply reflect alcohol use behaviors that would otherwise be observed in the absence of social media.

Given how much time adolescents spend on social media in conjunction with the multiple ways (eg, messaging and photos) and opportunities to communicate about alcohol on social media, social media are likely to be important social influences related to alcohol use [54-56]. Research has shown that social media contributes to the salience and amplification of drinking events, as people are now exposed to new and different drinking groups and locations than they would be offline [57]. In fact, research has shown that adolescents report having more social media contacts than their offline peers [58], which expands exposure to peer risk behavior, including alcohol use. In addition, research has shown that an increase in the number of Facebook friends is significantly associated with an increase in one's own alcohol displays [59]. This becomes particularly important because both experimental and longitudinal research indicates that viewing social media profiles that contain alcohol displays is related to increased risky drinking cognitions [19] and high-risk alcohol use [60,61]. In essence, exposure to alcohol content posted by friends can cultivate unfavorable cognitions such as norms, perceived vulnerability to risk, and attitudes that are then rapidly spread through the web-based networks and contribute to the adoption of risky beliefs and behaviors among other adolescents. Several studies suggest that adolescents use social media to reconstruct negative and risky drinking practices into positive outcomes [54,62] to avoid acknowledging any implications of or reference to negative consequences associated with drinking [63]. Furthermore, research suggests that adolescent viewers are likely to accept their peers' social media posts as accurate representations of their offline experiences [64].

Research has shown that alcohol use and alcohol-related displays on social media are common among adolescents and that these displays are associated with problematic drinking; therefore, alcohol intervention research for this age group should include content directly related to these social media influences on alcohol use. Previous research has shown that parents have limited insight into the types of experience teens have on the internet [65,66]. Although research indicates that many parents try to monitor social media activities [67], a study has documented the limited efficacy of such attempts [68], concluding that the most effective way for parents to gain insight into their teens' web-based activity is for their teens to tell them [69]. This effort to explain the role of parents as socialization agents in teens' media use is referred to as parental mediation [70].

Two broad dimensions of parental mediation have been examined: restrictive mediation and instructive mediation [71]. Restrictive mediation refers to parents limiting their children's access to media or setting rules in terms of appropriate media content and the amount of media exposure permitted [72]. Instructive mediation refers to parents explaining and discussing undesirable aspects of media consumption, suggesting proper ways to use media, and overall communication meant to help their teens understand the nature and possible impact of media messages [70,73,74]. The parental mediation literature suggests that instructive mediation is more effective than restrictive mediation in reducing undesirable influences of social media on teens (refer to the study by Valkenburg et al [74]), partly because instructive mediation is based on conversation and critical discussion between parents and teens, which is more likely than control-based restrictive mediation to cultivate critical thinking skills and skepticism in teens [73].

In general, the observational nature of traditional media channels (ie, television, film, and print), meant that audiences were passive observers who were not able to influence the content they were observing [75]. However, social media has created a culture in which users can participate in content creation and sharing. As social media are more interactive and repetitive than other types of media (eg, television, film, and print), contain images of actual peers, and content can both be created and consumed, the risks related to social media may be greater than those related to other forms of media [19]. Although many parents may feel comfortable with the social media that their children are using, others may find it difficult to relate to their digitally savvy children for several reasons. First, parents may lack a basic understanding of social media socialization [76]. In addition, most parents may not understand that for many adolescents, their web-based lives are an extension of their offline lives, and as a result, there may be a disconnect between parents and their teens in the understanding of social media use [77]. As such, strategies used for general parental mediation of more traditional forms of media (ie, television, film, and print) may not be adequate to account for the unique risks presented by social media. In fact, research has argued that existing parental mediation techniques grounded primarily on television and film media have fundamental inadequacies when applied to media such as websites, social media, and mobile apps, as they do not account for the immersive web-based environments and mediated communication innate to social media [25]. Furthermore, most parental mediation studies involving social media focus on issues such as privacy [71,78] and cyberbullying [79] and do not take into account the role that social media plays in relation to underage alcohol use.

Only 2 studies have provided an alcohol intervention via social media [80,81], but they did not address any content related to social media. Rather, these studies used social media as a mode of intervention delivery. A systematic review that focused on the use and effectiveness of social media in health behavior change found that Facebook is the most commonly targeted social media in this type of intervention [82], despite teens being on many other social media. Weight loss and eating behaviors were the most commonly targeted health behaviors, with only a few studies targeting health risk behaviors (smoking and

condom use). None of the studies identified in the review targeted alcohol use, indicating a substantial need for this research. We are unaware of any study that has tried using parental intervention as a strategy to reduce alcohol use and alcohol displays on social media.

Development of a Web-Based PBI Focusing on the Role of Social Media in Adolescent Alcohol Use

PBIs are universal prevention programs that target adolescent behaviors but use the parents of adolescents as change agents [14]. This is done by advising parents on how to engage in instructive parental mediation to become effective change agents and to help parents implement best practices in communication. For example, parents sometimes know less than their children do about new technologies or popular topics [83], and parents may be uncomfortable or unwilling to discuss content that may lead to conflict. Therefore, the goal of PBIs for alcohol use is to encourage parental mediation by educating parents about the current landscape related to alcohol, issues their teens may be facing, and advising parents on how to initiate and conduct healthy communication.

At the core of PBI research is the assertion that parents are a major source of health information for their teens and that the majority of teens report being very satisfied with the information they receive from their parents [84]. Moreover, providing parents with information to share with their teens will allow teens to discuss and clarify, which would not occur if teens were provided the information directly. According to national agency, Mothers Against Drunk Driving, in 2017, a total of 9100 parents attended in-person workshops (Mothers Against Drunk Driving, email, April 10, 2018). This indicates that despite their busy schedules and competing tasks, parents are interested in receiving more information about how to talk to their teens about substance use. Therefore, a PBI that includes information about alcohol and social media is likely to be an important source for parents and their teens to receive and share information related to social media.

In a typical PBI, handbooks on how to communicate with adolescents about alcohol are mailed to the parents of adolescents (most commonly incoming college freshmen) [12,14,27,85]. Specifically, the theory underlying PBIs emphasizes 2 key components: style and content. Parents are instructed to use an empathic and conversational communication style while providing accurate information about student alcohol consumption (eg, biological aspects). Components generally included in PBIs involve those based on the theory of planned behavior (eg, attitudes, norms, and perceived behavioral control) and those based on facilitating healthy communication and relationships between a teen and their parent [14]. A major strength of PBIs is that parents can tailor the content and timing of communication to adolescents based on their knowledge of their child's strengths, weaknesses, maturity level, and current alcohol use. This feature of PBIs respects the diversity of adolescents and their experiences and recognizes that not all adolescents respond identically to the same information. A PBI, as opposed to formal workshops, provides parents with more time flexibility and permits them to work at their own pace and during times that they choose.

This approach has proven successful in reducing the odds that nondrinking high school students will initiate alcohol use during the first year of college [12] as well as reducing general alcohol consumption [12,14,15,27,86]. Although these effects may be modest, given the ease of dissemination, low cost, and complex nature of underage drinking, PBIs are supported as a model resource in the National Institute on Alcohol Abuse and Alcoholism's College Intervention Matrix and by the Surgeon General [2]. A systematic review [26] supported the idea of involving parents in prevention programs. Across studies and concepts, they found evidence that participating in PBIs had desirable effects on parenting measures such as rule-setting, monitoring, and parent-child communication as well as the prevention and reduction of adolescent substance use.

Despite promising findings for PBIs to reduce adolescent alcohol use, one limitation of this body of work is that they do not consider the increasing role that social media plays in the lives of adolescents and how this is associated with their alcohol use. In addition, most PBIs consist of static formats such as downloadable or mailed parent handbooks [15,26,27] as opposed to web-based formats, and therefore, they do not provide continued support throughout the PBI. Furthermore, the nature of social media lends itself to creating PBI materials that can give parents a realistic view of the web-based environments that their children are navigating. We know that there is a strong relationship between alcohol use and viewing and creating alcohol displays on social media and that parents are still an important channel of communication about alcohol use and social media for adolescents. The next logical step is to determine whether PBIs, and in particular a PBI containing both web-based content and SMS text message prompts, can be developed to reduce both alcohol use and risky cognitions related to alcohol displays on social media. This is the main goal of this intervention protocol.

Methods

Study Design

This study will involve conducting a pilot study with 100 parent-teen dyads to determine the feasibility, acceptability, and preliminary effect sizes (to estimate power and sample sizes for a future full-scale randomized controlled trial [RCT]) of the developed social media PBI. A total of 100 parent-teen dyads will be randomized into 2 groups: a group receiving the newly developed web-based social media PBI or an active control group (treatment as usual [TAU] [2]). We hypothesize that the social media PBI, relative to TAU, will be rated by parents and teens as more *feasible* (number of eligible participants, number of parents who gave consent, number of teens who gave consent, time taken to achieve planned recruitment and enrollment goal, and rate of study attrition) and more *acceptable* (measured at 1-month follow-up with specific postintervention survey items, ie, proportion of parents and teens who find the intervention acceptable; ease of interacting with social media PBI content; relevance of material; finding content helpful, beneficial, and important; ratings of individual modules and components of the social media PBI; the proportion of parents and teens who would recommend the study to other families; and the proportion of

parents and teens who found the social media PBI to be favorable overall) in relation to active control or TAU. We further hypothesize that teens and parents in the social media PBI condition will report more positive communication about alcohol and social media at 1- and 6-month follow-up relative to TAU.

Parent hypotheses: We hypothesize that at 1- and 6-month follow-up, parents in the social media PBI condition will report greater knowledge about alcohol as well as the role of social media in alcohol use relative to TAU.

Teen hypotheses: We hypothesize that teens in the social media PBI condition will report less drinking, fewer alcohol-related negative consequences, less favorable attitudes toward posting about alcohol on social media, greater perceived vulnerability to the risks of posting alcohol displays on social media, and decreased normative perceptions about how many teens post alcohol displays on social media relative to TAU at 1- and 6-month follow-up.

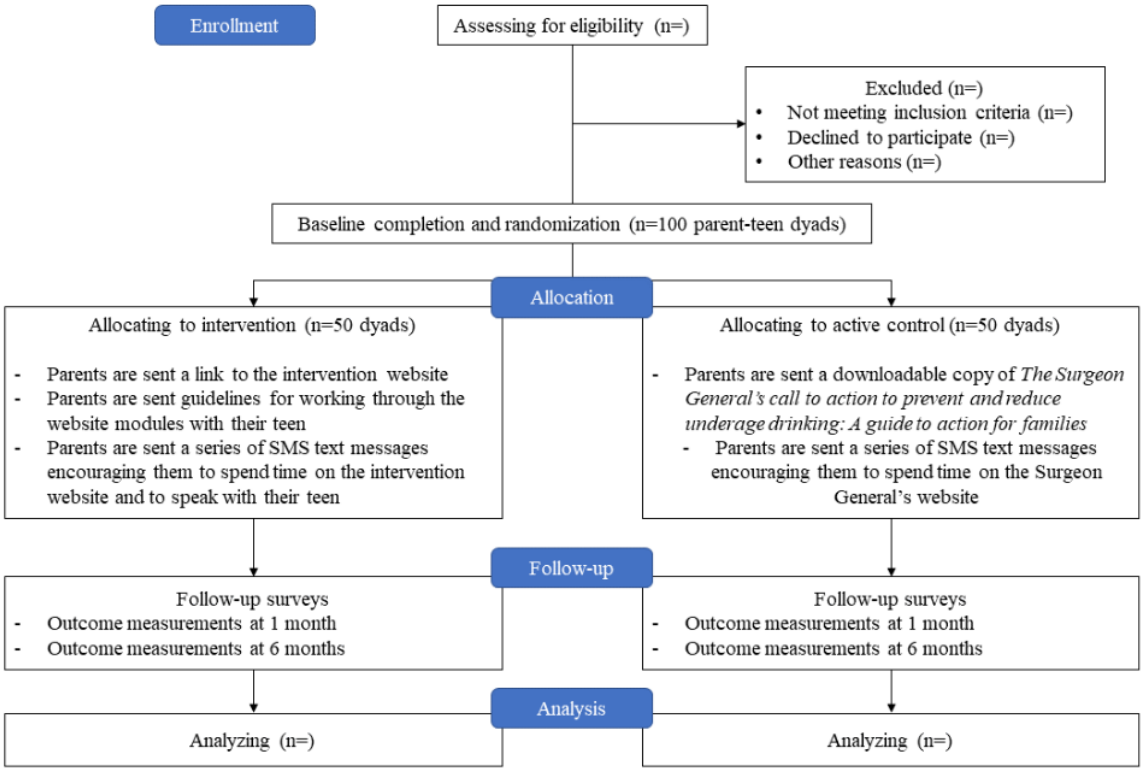
Ethics Approval

This study was reviewed and approved by the North Texas Regional Institutional Review Board (#2021-124). All participants will sign an approved consent form in accordance with the ethical standards of Helsinki.

Recruitment

We will use a multimethod approach to reach a wide cross section of parents of adolescents and young adults from Texas, including web-based and electronic newspaper advertisements, electronic flyers, and social media. Web-based advertisements will be placed in local and social media outlets frequented by those likely to have children aged 15 to 20 years. We will also recruit parents through community organizations in major cities in Texas. Contacts at community organizations will be initially contacted via email by project staff. In this email, the project staff will provide information about the study and encourage further questions. If they agree to share study information with their members, the project staff will send them the consent link and QR code. Similar emails will be sent to high school administrators to recruit the parents of students. We will stratify recruitment based on age, gender, and ethnicity, recruiting equal number of parents with adolescents in each age category (ie, 15, 16, 17, 18, 19, and 20 years) and targeting equal number of males and females in each age group. We will recruit all minority parents to be above the local census estimates. Figure 1 shows the workflow diagram.

Figure 1. Pilot study workflow diagram.



After receiving information about the study, participants will be presented with the web-based informed consent statement that covers the screening survey, intervention, and follow-up surveys. If eligible, individuals will be asked to provide an electronic signature before being directed to participate in the web-based screening survey, which will determine whether they are a good fit for the study (refer to Textbox 1 for the inclusion criteria). Only those participants who sign both the web-based consent and assent form and Health Insurance Portability and Accountability Act authorization form (one for themselves and one for their child if the child is aged 15-17 years) will be routed to the Screening Welcome Page. Parents are informed in the parent consent form that their teen will be asked to sign their own consent and assent form to indicate whether they want to

participate in the research study. Once a parent has been deemed eligible and has provided contact information (and consent and Health Insurance Portability and Accountability Act form for their teen aged 15-17 years), their teen will be sent a link (using the contact information provided by their parent) to the consent form and screening survey. As with the parents, adolescents will be presented with an web-based informed consent statement and will be asked to provide an electronic signature before being directed to participate in the web-based screening survey, which will determine whether they are a good fit for the study (Textbox 1).

We will use previously successful strategies to maximize retention [87-91]. First, study incentives will show that time and effort are appreciated. We pay for all assessments (with bonuses) to encourage high completion and send all participants a variety of nominal items intended to offset the cost of completing assessments, thus promoting participation. Second, data collection strategies allow participants to complete surveys using smartphones or computers. Third, we will call participants before data collection sessions (eg, 1- and 6-month follow-up surveys) as a reminder of an upcoming survey and to stay connected with the project staff. Fourth, we will gather contact information at each time point and provide a toll-free number, study email address, and study website with a link for participants to update the contact information. Fifth, we will use persistent monitoring to keep track of barriers to participation. These methods have proven effective in our ongoing successful study, retaining adolescent and young adult participants for over 2 years.

Textbox 1. Inclusion criteria.

Inclusion criteria for parents or legal guardians

- Have a child aged between 15 and 20 years who currently lives with them
- Believe that their child is active on at least one social media platform
- Live in Texas
- Provide a valid email address
- Own a cellphone with SMS text messaging capabilities and be okay with receiving messages
- Provide consent for their child if the child is aged 15 to 17 years
- Provide valid contact information for their child
- Be willing to participate in a study that involves a parenting program and a series of web-based surveys with their teen
- If multiple parents are interested, they will be instructed to choose one parent to participate

Inclusion criteria for teens

- Have an eligible parent with whom they currently live
- Be aged between 15 and 20 years
- Live in Texas
- Be active on at least one social media platform
- Provide a valid email address
- Own a cell phone with SMS text messaging capabilities and be okay with receiving messages
- Be willing to complete three 45-minute web-based surveys over the course of 6 months

Procedures

After both the parent and teen in each dyad have completed their respective baseline surveys, the parent-teen dyads will be randomly assigned to one of the following 2 conditions: PBI or control. Parents in the intervention condition will be sent an email and a SMS text message containing a link to the PBI website along with information explaining the study and providing guidelines for working through the modules with their teens (refer to Textbox 2 for an overview of the specific modules; see Figure 2 for sample module content). Parents may revisit the web-based PBI as many times as they like over the course of a month before the 1-month survey. Parents will also be sent a series (4 total) of SMS text messages encouraging them to spend time on the web-based PBI and encouraging them to speak with their children. Parents in the control condition will be sent an email with a downloadable copy of *The Surgeon General's Call to Action to Prevent and Reduce Underage Drinking: A Guide to Action for Families*. This manual is publicly available on the Surgeon General's website [2]. Parents in the control condition will be sent a series of SMS text messages (4 total) encouraging them to spend time reviewing the Surgeon General's guide. Parents in the control condition will be provided the link to the intervention condition website at the end of study completion.

Parent-teen dyads who meet the inclusion criteria and pass phone verification (to confirm identity) will be emailed and texted a baseline survey link. The baseline survey will include questions about demographics, social media literacy, parenting, drinking and drug use, drinking cognitions, mental health, and other health behaviors and will take approximately 45 minutes to complete. The questions in the assessments will also include

topics about sexual orientation, gender identity, religion, and relationship status. For those in the intervention group, items in the 1-month follow-up survey will assess satisfaction with the intervention website. If we do not receive the completed assessment at each follow-up (baseline assessment, 1-month assessment, and 6-month assessment), we will periodically send reminders—via email (up to 6), SMS text messages (up to 6), and phone or voicemail (up to 5). Parents and teens can earn US $25 for the baseline assessment, US $35 for the 1-month assessment, and US $40 for the 6-month assessment, meaning that all participants can earn up to US $100.

Textbox 2. Parent-based intervention's modules and descriptions.

Module 1: communication matters

- Parents will learn about facts and myths related to communicating with their teen as well as review tips and strategies to effectively initiate and maintain conversations.

Module 2: your teen's world

- Parents will gain insight into the important role of social influence on teen decision-making.

Module 3: talking about social media with your teen

- Parents will learn about specific tips and strategies related to talking with their teens about their social media use.

Module 4: media literacy for teens

- Parents will review the importance of teaching their teens social media literacy skills and gain tips and strategies on teaching and practicing these skills.

Module 5: social media, alcohol, and your teens

- Parents will be exposed to information related to the impact of alcohol content their teen may view or share on social media on their behavior and learn tips and strategies for approaching these topics with their teen.

Module 6: social media and other health risk behaviors

- This module will review other concerns (drug use, sexual behavior, mental health, and cyberbullying) that parents may also want to discuss with their teens.

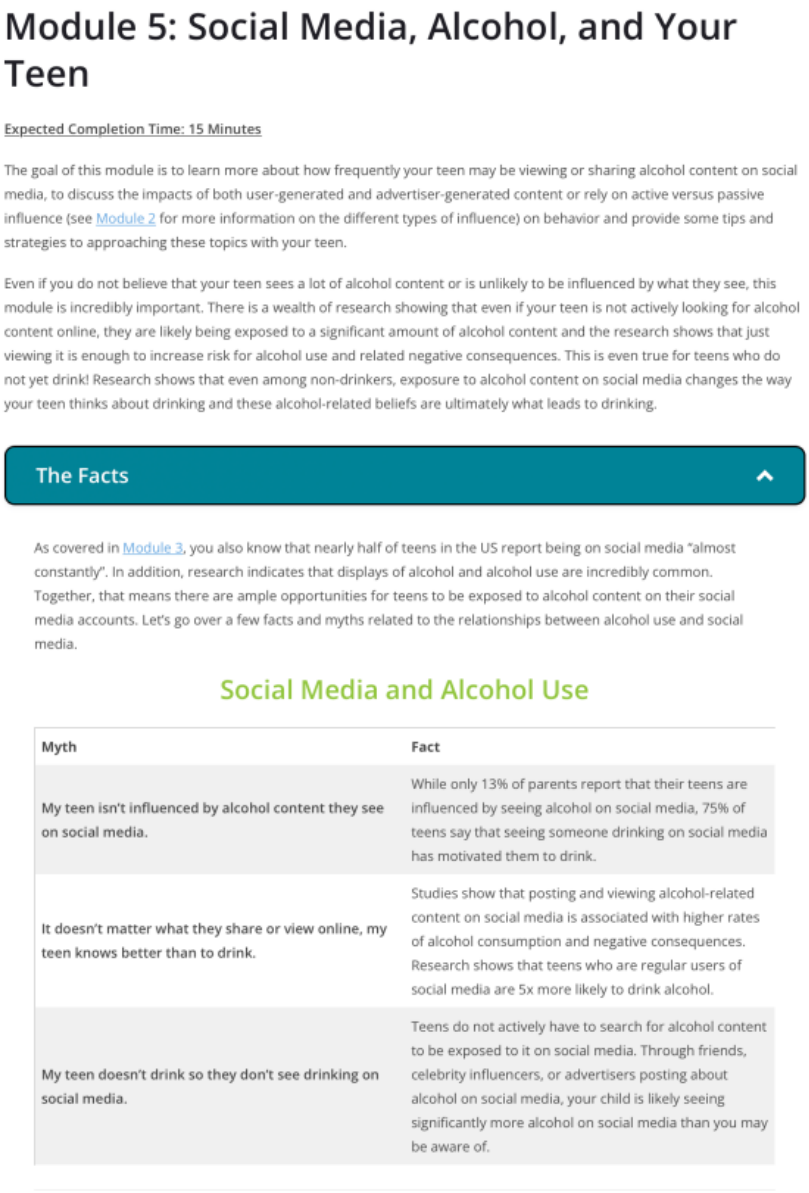
Module 7: closing thoughts

- A summary of topics covered and final tips and strategies will be provided.

Module 8: resources

- Additional resources related to the topics discussed across all modules are available here.

Figure 2. Sample module content.



Measures

Behavior will be reported over lifetime (baseline) and the past month (1- and 6-month follow-up) to reduce problems with retrospective recall and overlap. All measures will be assessed at baseline and 1- and 6-month follow-up, unless otherwise noted.

Demographics

Demographics will include age, biological sex, gender, race, ethnicity, height, weight, and family history characteristics.

Parent-Teen Relationships

Parent-teen relationships will be evaluated in terms of parent-teen communication regarding both alcohol and social media (Cronbach α=.53-.75) [10]. To determine the nature of parental involvement and monitoring of teens, parental monitoring will be assessed using the Parental Monitoring and Knowledge Scale (Cronbach α=.81) [92] and the Parental Monitoring of Social Media measures (Cronbach α=.67-.88) [93].

Social Media Use

Both parents and teens will be asked about their own social media use by answering questions on how often they check different social media platforms, their exposure to alcohol-related social media content, their own alcohol-related communication on social media, and their motives for using social media. Parents will also report perceptions of their teen's social media use with the same questions.

Alcohol and Other Substance Use

Parents and teens will be asked questions regarding their alcohol and substance use. Family history of alcohol (baseline only) as well as lifetime and past-year alcohol use (baseline only) will be assessed [94]. Drinking will be assessed using the Daily

Drinking Questionnaire and the Quantity Frequency Index (Cronbach α=.73) [95-97] and the Alcohol Use Disorders Identification Test (Cronbach α=.85) [98,99]. Alcohol consequences will be assessed using the Young Adult Alcohol Consequences Questionnaire (Cronbach α=.79) [100]. Marijuana use will be measured using items including lifetime, past-year, and past-month marijuana use [94]. Other substance use will be assessed for lifetime and past-month use with the Customary Drinking and Drug Use Record (Cronbach α=.70-.94) [101].

Satisfaction With the Intervention

Finally, both parents and teens in the intervention group will be asked to complete a 1-month satisfaction questionnaire related to their experience, perceptions, and interactions with the intervention website. In particular, parents will be asked how often they visited the web-based PBI and its specific modules; how they feel about the PBI and the modules in terms of acceptability (eg, acceptability of content delivery method), usability (eg, ease of viewing and interacting with PBI content), relevance (eg, relevance of material), and helpfulness (eg, finding content helpful, beneficial, and important); and whether parents would share the information in the PBI with anyone else. Both parents and teens will be asked whether they would like to have additional conversations on this topic, if they would recommend the study to others, and whether they found the program to be favorable overall.

Statistical Analyses

To evaluate the pilot study proposed in this protocol, we will examine recruitment and retention rates, parents' postintervention feedback as measured at 1-month follow-up (ie, accessible, usable, convenient, relevant, and helpful), teens' rates of alcohol initiation and use and alcohol-related negative consequences, and parents' and teens' reports of alcohol and social media–related communication that will provide base rates and variance in outcomes to determine adequate power for a future full-scale efficacy RCT.

Feasibility will be assessed by the proportion of parents who meet the inclusion criteria and enroll for the study, the proportion of teens who meet the inclusion criteria and enroll for the study, and the proportion of parents and teens who complete the social media PBI at the 1-month follow-up. Finally, the time taken to recruit our target enrollment number will also be used as an outcome of feasibility.

Acceptability will be assessed with parents' and teens' responses at 1 month. Acceptability will be determined by (1) the proportion of eligible parent-teen dyads enrolled, with 80% (100/125) of eligible dyads agreeing to participate; (2) the proportion of participants (both parents and teens) who find the intervention acceptable (eg, acceptability of content delivery method), usable (eg, ease of viewing and interacting with PBI content), relevant (eg, relevance of material), and helpful (eg, finding content helpful, beneficial, and important); (3) parents' and teens' ratings of individual modules in the social media PBI; (4) whether parents and teens would like to have additional conversations on this topic; (5) whether parents would share the information in the PBI with anyone else; (6) the proportion of parents and teens who would recommend the study; and (7) the proportion of parents and teens who found the program to be favorable overall. Acceptability will be specifically determined if acceptability for the social media PBI is higher than that for the control and if at least 80% of responses in each domain are rated a 4 or higher (out of 5).

This pilot will *explore treatment differences and determine preliminary effect sizes* for teens' drinking as well as parents' knowledge about alcohol and social media, and parent- and teen-reported outcomes will be analyzed in separate models. All models will have 3 repeated measures (ie, baseline and 1- and 6-month follow-up), yielding up to 300 level 1 observations (repeated measures) across 100 level 2 cases (teens or parents). Before inferential statistics, univariate and bivariate descriptive statistics will be used to assess the distributions and simple associations among the variables. Primary teen-reported outcomes are alcohol use and negative consequences (both count outcomes) as well as cognitions (attitudes, norms, and perceived vulnerability related to social media alcohol displays; all modeled as normally distributed outcomes). Primary parent-reported outcomes will be knowledge about alcohol and social media (modeled as normally distributed outcomes). Given the repeated-measures design, generalized linear mixed models [102] will be used. Generalized linear mixed models (ie, hierarchical generalized linear models) allow for nonnormal outcomes and missing data.

Results

This research was funded in August 2019, and the pilot RCT phase was approved by the institutional review board in January 2022. Recruitment and enrollment will begin in August 2022. The findings will be published in peer-reviewed journals and presented at international, national, or regional academic and professional meetings and conferences. This study is expected to conclude in August 2023.

Discussion

Principal Findings

The central goal of the proposed study is to develop, refine, and pilot a web-based PBI to reduce both high-risk social media cognitions and alcohol use among adolescents. Despite PBIs for alcohol use being widely accepted as efficacious, they do not take into account the growing importance of social media. Given how much time adolescents spend on the web and that their social media behavior is linked with alcohol use, PBIs could be more efficacious by addressing these social media sources of social influence. In preparation for large-scale prevention projects, pilot studies are needed to engage and solicit input from participant populations to empirically test and establish evidence for the feasibility and acceptability of intervention protocols. As such, this study will make important strides toward developing, refining, and establishing early-stage efficacy for a web-based social media PBI that can be tested in future randomized clinical trials.

This study has the potential to open doors to future studies examining the clinical implications of an efficacious PBI to reduce alcohol use and high-risk cognitions about alcohol

displays on social media. An intervention designed to reduce an individual's risky cognitions or beliefs based on alcohol displays that they view could, in turn, reduce risk cognitions among the individual's web-based social media peer networks. Reducing these high-risk cognitions among one individual has the potential to reduce the number of displays their web-based peers view and thus potentially reduce peers' drinking cognitions and ultimately behavior. This network-based cascade of peer influence can potentially reach thousands of adolescents from only a few initial participants. Determining an efficacious way to reduce high-risk alcohol display cognitions affords future research the opportunity to make use of social network-based interventions; thus, the proposed research has great potential to serve as a catalyst for future research.

Furthermore, because the social media PBI will be designed to display appropriately on any web-enabled device, including smartphones and tablets, there is strong potential to develop an app-based product (through commercial support or a subsequent grant) that could be implemented in different contexts, such as high school or college alcohol prevention, or as a stand-alone product. The knowledge gained from testing the feasibility, acceptability, and pilot of the developed social media PBI has a significant capacity to be generalized to interventions aimed at reducing other high-risk health behaviors (eg, marijuana use and other substance use) and could provide evidence that providing more PBI modalities, as opposed to being disseminated via emailed handbooks as is current practice, leads to greater reach, sustainability, and real-world impact. The prevalence of alcohol use in underage adolescents and young adults continues to be a public health concern [1]. People aged 12 to 20 years drink 11% of all alcohol consumed in the United States, with more than 90% of this alcohol being consumed in the form of heavy episodic drinking [103]. Excessive drinking is responsible for more than 4300 deaths among underage youth each year and cost the United States US $24 billion in economic costs in 2010 [104]. Thus, this study has a high potential to exert a sustained, powerful impact on the field of adolescent and young adult interventions for alcohol use, which remains prevalent and problematic.

In short, the proposed research has high potential for impacting the field of adolescent alcohol prevention, as it is both timely and innovative. With adolescents spending increasingly more time on social media and being exposed to more alcohol displays, and with research showing the association with increased drinking, it is imperative that interventions address the influence of social media. The proposed study is innovative, as it will be the first PBI to focus on the role of social media in adolescent alcohol use. Furthermore, because the proposed PBI will be designed to target alcohol displays as they pertain to multiple social media, not specific to any single social media, the PBI will be relevant to a wider group of adolescents as well as those who use more than one social media, and the intervention will continue to be relevant as social media come and go in popularity among adolescents. In addition, this study is particularly innovative, as it combines efficacious interventions based on parent-teen communication with the timely addition of alcohol displays on social media. Focusing the intervention on parent delivery means that the intervention can be available to adolescents and young adults in high school or following high school graduation. Under the National Institute on Alcohol Abuse and Alcoholism's strategic plan, there is a request for research that expands screening and brief interventions to adolescent and young adult populations beyond that of 4-year college students [105]. Following high school, many young adults do not pursue postsecondary education or do not have access to brief interventions (as typically offered through university health centers). A PBI would allow delivery to parents of adolescents and young adults regardless of postsecondary attendance. Another particularly innovative aspect of this protocol is that unlike most PBIs that are sent to parents in a static manual format, the nature of the social media PBI (ie, the social media PBI being web-based with content and supplemented with SMS text messages) has the potential to make PBIs even more efficacious, as the parents will have continued support as they work through the social media PBI content with their teens.

Limitations

No study is perfect; therefore, it is important to acknowledge potential limitations. First, a meta-analysis showed that the use of incentives to recruit for web-based research may lead to selection effects, which might impact external validity [106]. However, considering that random assignment ensures relatively similar characteristics across study conditions, selection effects are typically not a problem for randomized trials [107]. Second, all data will be collected in a single state, namely, Texas. It is likely that there exist different norms for adolescent alcohol consumption in different states and in different countries, which affect actual adolescent alcohol consumption and parental communication about alcohol consumption. Hence, the results may not be generalizable, and it is important to test this protocol in different settings when moving on to large-scale testing. Finally, considering that this is a small-scale pilot study, we did not design this study to be fully powered. Nevertheless, our results will provide preliminary effect sizes to calculate the power for a subsequent full-scale RCT.

Conclusions

This study addresses the critical gap in the literature that PBIs do not take into account the large role that social media plays in the lives of adolescents and in relation to their alcohol use. Therefore, the main goal of our research is to determine whether a PBI can reduce both alcohol use and risky cognitions related to alcohol displays on social media. To achieve this goal, this research will collect pilot data to determine the feasibility, acceptability, and preliminary effect sizes of the developed social media PBI.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-reviewer report from the Epidemiology, Prevention and Behavior Research Review Subcommittee - National Institute on Alcohol Abuse and Alcoholism (NIAAA) Initial Review Group (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 196 KB - resprot_v11i5e38543_app1.pdf]

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Abbreviations

NIAAA: National Institute on Alcohol Abuse and Alcoholism
PBI: parent-based intervention

RCT: randomized controlled trial
TAU: treatment as usual

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Protocol

An Integrated mHealth App for Smoking Cessation in Black Smokers With Anxiety: Protocol for a Randomized Controlled Trial

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Abstract

Background: Black smokers have greater difficulty in quitting and higher rates of smoking-related diseases and disabilities than the general population. The smoking disparities experienced by this group are, in part, a consequence of multiple chronic life stressors (eg, racial discrimination) that engender increased exposure to interoceptive stress symptoms (eg, anxiety), which can ultimately lead to smoking as a means of immediate emotion regulation.

Objective: This study aimed to culturally adapt and initially test a novel mobile intervention (ie, Mobile Anxiety Sensitivity Program for Smoking [MASP]) that targets anxiety sensitivity (AS; a proxy for difficulty and responsivity to interoceptive stress) among Black smokers. The MASP intervention is culturally informed to address interoceptive stress management difficulties among Black smokers and is thus hypothesized to facilitate smoking cessation.

Methods: In phase 1, a total of 25 Black smokers with elevated AS will be administered MASP for 6 weeks. Following the completion of phase 1, we will further refine the MASP based on qualitative and quantitative data from participants to produce the final MASP iteration. In phase 2, a total of 200 Black smokers with elevated AS will be enrolled and randomly assigned to receive nicotine replacement therapy and either the smartphone-based National Cancer Institute QuitGuide app for standard mobile smoking cessation treatment or the MASP intervention. All participants in phases 1 and 2 will be enrolled remotely and will complete a web-based study screener; smartphone-based baseline assessment; daily smartphone-based ecological momentary assessments for 6 weeks; phone-based end-of-treatment qualitative interviews; and smartphone-based follow-up assessments at postbaseline weeks 1, 2 (quit date), 3, 4, 5, 6, 28, and 54 (weeks 28 and 54 follow-ups will be completed by phase 2 participants only). The MASP intervention is intended to offset barriers to treatment and encourage treatment engagement via smartphones.

Results: This project was funded in September 2020. Phase 1 data collection began in January 2022. Phase 2 data collection is scheduled to begin in July 2022.

Conclusions: If successful, data from this study will support culturally informed treatment approaches for Black smokers and, pending findings of efficacy, provide an evidence-based mobile intervention for smoking cessation that is ready for dissemination and implementation.

Trial Registration: ClinicalTrials.gov NCT04838236; https://clinicaltrials.gov/ct2/show/NCT04838236

International Registered Report Identifier (IRRID): DERR1-10.2196/38905

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KEYWORDS

smoking cessation; treatment; Black; African American; anxiety sensitivity; mHealth; just-in-time adaptive intervention; mobile phone

Introduction

Black African American individuals are a tobacco-related health disparity group [1]. The prevalence of smoking among Black adults is 14.4% [2], exceeding that of non-Hispanic White individuals [2], regardless of socioeconomic status [3]. Although Black smokers smoke fewer cigarettes per day [4] and tend to begin smoking later in life than non-Hispanic White individuals [5], they evince greater levels of nicotine dependence [6] and serum cotinine [6-8] and are less likely to maintain abstinence despite more quit attempts [9]. Less quitting success may potentiate mortality rates for cardiovascular disease and other illnesses, which are overrepresented among this group [10]. A major contributing factor to smoking among Black adults appears to be their increased exposure to interoceptive stress symptoms, potentially stemming from and exacerbated by chronic stress related to systemic racism and racial discrimination [4,11-16].

Black adults are a health disparity group for interoceptive problems, including somatic symptoms, anxiety, stress, and pain [13-18], and evince stronger relations between negative emotional states and somatic experiences than White adults [19]. This is notable as Black adults diagnosed with anxiety disorders experience higher rates of hypertension, a condition for which Black adults are almost twice as likely to be diagnosed than White adults [20]. Black adults' increased awareness of the negative outcomes of physical illnesses may further amplify somatic anxiety and interoceptive distress [21,22]. Anxiety sensitivity (AS) is among the most prominent cross-cultural constructs related to interoceptive distress. AS is a malleable, cognitive-affective factor that reflects the tendency to respond to interoceptive distress and anxiety [23,24]. AS is related to but distinct from negative affectivity and trait anxiety [24-30] and has demonstrated racial and ethnic, gender, age, and time invariance [27,29,31-33].

Smokers with elevated AS report greater tendencies to smoke to reduce negative affect, hold stronger beliefs that smoking will reduce negative affect, smoke in an inflexible manner in response to negative mood, perceive greater barriers to cessation, and experience increased expectations for adverse emotional distress during smoking deprivation [34-37]. The effects of AS on smoking seem to be independent of negative affect states such as anxiety or depression symptoms [38-40]. Smokers with high AS experience more intense nicotine withdrawal and craving during quitting, and higher levels of AS are related to greater odds of early lapse and relapse across clinical and nonclinical samples [41-43]. Withdrawal symptoms might be particularly salient in Black smokers with higher AS, as they may be more apt to perceive these internal sensations as uncontrollable because resources to regulate withdrawal symptoms (ie, adaptive-cognitive and behavioral skills) are likely diminished because of chronic stress exposure (eg, microaggressions, racism, and stress-related burden because of racial discrimination) [44,45]. In turn, Black adults with higher AS may be motivated to smoke to reduce emotional and interoceptive distress.

AS reduction has been integrated into in-person substance use treatment programs among largely non-Black samples [46]. Such programs, originally developed by our team [47,48] and now replicated by other researchers [49-52], have found that reducing AS via cognitive behavioral therapies before quitting increases the odds of smoking cessation [53,54]. Although such effects tend to be the most robust among smokers with higher AS [55], reduction of AS, even among smokers with moderate levels of AS, is helpful in reducing tobacco-related stressors such as withdrawal [55] and improving mental health [56]. However, all previous AS reduction work for smoking has thus far been conducted via in-person approaches within non-Black samples, except for our successful small-scale pilot study, which included a large proportion of Black smokers (66.7%) [57]. Given that smoking can produce perceived or objective acute anxiolytic effects [58], Black smokers with high AS may be more likely to return to smoking following a quit attempt, in part, to alleviate abstinence-induced increases in anxiety, underscoring the need for a culturally tailored intervention to address internal agitation in the context of smoking cessation treatment.

To date, no smoking cessation treatments for Black smokers have focused on sensitivity to interoceptive stress despite the importance of somatic symptoms, including anxiety, stress, and pain, among this population. Furthermore, previous efforts to evaluate the effectiveness of culturally targeted smoking cessation programs for Black smokers have mainly used minimal intervention strategies and group counseling and were nonrandomized trials [59]. We developed and preliminarily tested our novel, integrated, smartphone-delivered intervention for interoceptive stress and smoking (ie, Mobile Anxiety Sensitivity Program for Smoking [MASP]) using a single-arm pilot trial design [57]. This intervention is based on theory and empirical evidence of the importance of interoceptive stress for smokers [60]. The purpose of our initial pilot of the MASP 1.0 (N=12; mean age 45 years; 66.7% Black) was to assess app engagement and determine whether there was an initial signal of app impact on cessation. Participants self-initiated interoceptive exposure exercises 6 times on average, self-initiated *relaxation exercises* 6 times on average, and accessed *treatment audio files* 2 times on average [57]. Biochemically verified abstinence was observed in 25% of the participants at the 6-week follow-up visit (4 weeks after quitting), which are striking and clinically important, given that (1) this was only the initial version of the treatment (MASP 1.0), and (2) smoking cessation success rates for Black smokers are typically low.

The objectives of this National Institute on Minority Health and Health Disparities–funded trial (U54MD015946) are to refine and evaluate the feasibility, acceptability, and efficacy of a novel, culturally tailored, smartphone-delivered MASP app for Black smokers. In phase 1, MASP 1.0 was refined and culturally adapted based on theoretical and empirical guidelines [61] and the initial participant feedback collected during the MASP 1.0 pilot to produce the MASP 2.0. Black smokers with elevated AS (N=25) will use the MASP 2.0 for 6 weeks (ie, the intervention period). Following the intervention period, participants will complete a qualitative interview, which, along with quantitative data and feedback from the community research advisory board as part of the Community Engagement Core of the health institute, will be analyzed to guide intervention refinement to produce MASP 3.0. In phase 2, we will conduct a randomized controlled trial (RCT) of 200 Black smokers with elevated AS who will be randomly assigned to either the MASP 3.0 or the smartphone-based National Cancer Institute (NCI) QuitGuide app, which is considered the smartphone-based standard of care for smoking cessation [62,63]. Mechanisms underlying the intervention effects, including the primary mechanism of AS and secondary mechanisms (ie, anxiety and depression symptoms, stress-based burden of racial or ethnic discrimination, and nicotine withdrawal or craving), will be evaluated. The indirect effects of the MASP intervention (vs QuitGuide) on smoking cessation via these mechanisms of change will be evaluated. Finally, we will explore whether stress associated with perceived racial discrimination, acculturation, ethnic identity, and COVID-19 may function as moderators of smoking outcomes.

Methods

Ethics Approval

The University of Houston (reference number: 12747) and the University of Oklahoma Health Sciences Center (reference number: STUDY00000360) institutional review boards approved the protocol presented in this study. This trial was registered at ClinicalTrials.gov (NCT04838236).

Study Eligibility

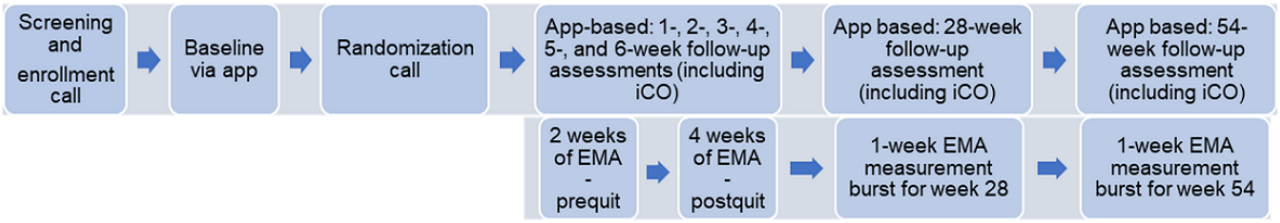
Adults aged ≥18 years are eligible to participate in this study if they self-identify as Black and report high AS (ie, Short Scale Anxiety Sensitivity Index [64] score of ≥5), daily smoking (minimum of 10 cigarettes per day) for at least 2 years, motivation to quit smoking (>5 on a 10-point scale) [65], willingness to complete all study surveys and assessments, willingness to use nicotine replacement medications (nicotine replacement therapy [NRT]; nicotine patch and lozenges), and desire to quit smoking 2 weeks after completion of the baseline survey and receipt of study materials. The exclusion criteria include current or intended participation in a concurrent substance use treatment program, ongoing psychotherapy of any duration directed specifically toward the treatment of anxiety or depression, not being fluent in English, current use of any pharmacotherapy or psychotherapy for smoking cessation not provided by this study, a legal status that would interfere with participation, cognitive impairment (assessed via the 6-item Cognitive Impairment Test [66]), being non-Black, and being aged <18 years. Those who participated in the previous phase of the study are not eligible to participate in future study stages.

Recruitment and Procedure

Participant enrollment in the study and all study procedures will be conducted remotely. We will advertise through community organizations that promote smoking cessation initiatives, social media, and internet outlets. Study screening will be completed via REDCap (Research Electronic Data Capture; Vanderbilt University) when a participant clicks on the study advertisement. Individuals who prescreen as eligible via the REDCap assessment will be phoned to provide informed consent and complete the final eligibility screening for the study. To reduce the likelihood of fraudulent enrollments in the study, potential participants will be required to text a picture of their pack of cigarettes in real time as evidence that they are smokers, and they will be required to text a picture of their ID or a piece of mail with their name and address on it. Persons who will be deemed eligible and willing to participate during the enrollment phone call will be provided with information about the purpose, goals, and procedures of the study and asked to download the Insight app (University of Oklahoma Health Sciences Center) onto their personal smartphone or mailed a smartphone if they do not have one that is compatible with the Insight platform.

Once the Insight app is downloaded, participants will be given a unique single-use code that will enable them to use the app to complete the baseline assessment on their personal or study-provided smartphone. After the baseline assessment is completed, participants will be mailed a Bedfont iCOquit smokerlyzer, which reports levels of carbon monoxide (CO) in expired breath to verify self-reported smoking status (phases 1 and 2). Upon receipt of the iCO, participants will complete a brief phone call with the study staff to review all app functions and be oriented to the iCO. In phase 2, REDCap will be used to randomize participants to the MASP 3.0 or QuitGuide during this brief call. Participants will then use the assigned intervention via the app for 6 weeks and complete daily ecological momentary assessments (EMAs) during the intervention period. App-based follow-ups will occur 1, 2, 3, 4, 5, and 6 weeks after the baseline for all participants; phase 2 participants will also complete follow-ups at 28 and 54 weeks after the baseline. All interactions with the QuitGuide and MASP apps will be date- and time-stamped, and the app feature use will be recorded for future analysis. All daily surveys and follow-up assessments (both treatment arms) will be completed using the Insight app, and a phone-based qualitative interview will be completed at the end of the 6-week intervention period. We have developed a system of procedures that includes contacting participants to encourage retention (ie, calling, texting, and emailing participants who have not completed follow-up assessments). Participants who will borrow smartphones will be asked to return them after the final follow-up assessment. In addition to randomization in phase 2, similar procedures will be followed in phases 1 and 2 (Figure 1).

Figure 1. Participant flow. EMA: ecological momentary assessment.



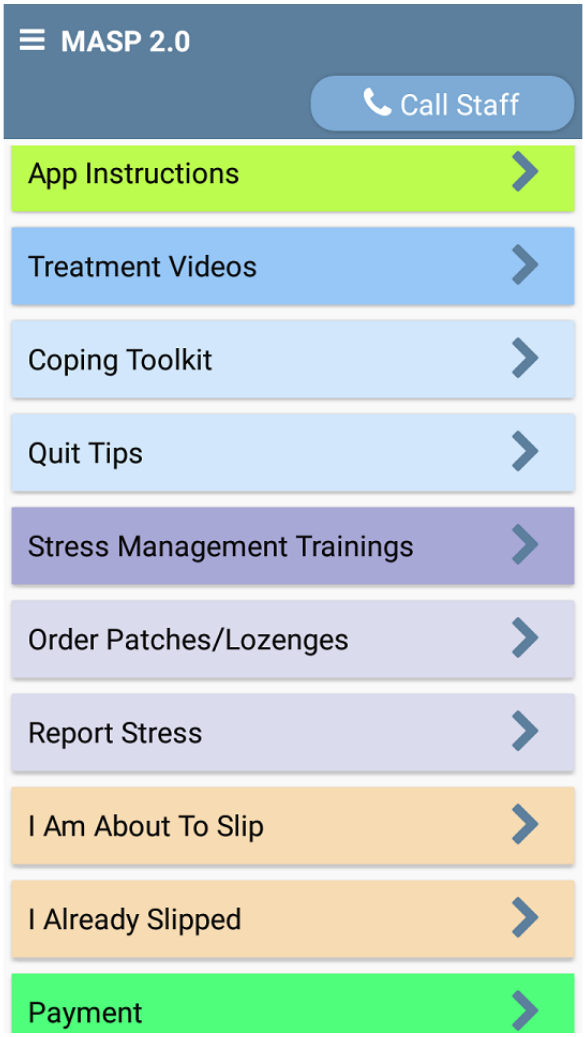
Following the completion of the smartphone-based baseline assessment in phase 2, we will block randomize participants by binary sex (assigned at birth) and baseline smoking level (rate per day) to ensure that the cell sizes are largely equivalent for maximally useful subgroup testing [67]. Variable-sized permuted block randomization (block sizes will vary from 6 to 10) will be used. Before data analysis, the balance of randomization will be checked and controlled for imbalanced factors.

Study Conditions

Both Conditions

Clinical guideline recommendations indicate that all smokers attempting to quit should receive pharmacotherapy [68]. Thus, the MASP (phases 1 and 2) and QuitGuide (phase 2) participants will receive a combination of NRT (transdermal nicotine patch and nicotine lozenges) during the first 4 weeks after quitting. Additional NRT (up to 8 additional weeks) may be requested beyond the first 4 weeks by clicking a button on the app home screen or clicking the *Call Staff* button on the app home screen (Figure 2). Note that 66% of those enrolled in one of our previous studies used a similar app button and feature to order the NRT [62]. We chose the patch and lozenges because of the extensive empirical literature supporting their effectiveness and safety, ease of use, and relatively benign side effect profile, as well as the increased efficacy of combination NRT [69,70]. The MASP app will send an encrypted email to alert the treatment team of NRT requests, and participants will be mailed an additional NRT.

Figure 2. The Mobile Anxiety Sensitivity Program for Smoking app.



NCI QuitGuide Condition

The NCI QuitGuide app is a free smartphone app available through Smokefree.gov. QuitGuide is one of the few apps that are consistent with many of the recommendations of the Clinical Practice Guidelines for quitting smoking [68]. Individual-level app feature use is accessible by request from Smokefree.gov server. The QuitGuide app aims to help smokers understand their smoking patterns and develop the skills needed to quit smoking. Participants who are randomly assigned to the QuitGuide condition will use their personal smartphone or receive a study smartphone if they do not have one, which will be preloaded with the QuitGuide app and preset for a quit date 2 weeks after randomization into an intervention group. Participants will receive information on how to use the QuitGuide app features during the randomization phone call. QuitGuide participants will also download an Insight EMA app stripped of all the MASP intervention features. Table 1 for a list of QuitGuide features.

Table 1. Comparison of phase 2 treatment conditions.

App components	MASP[a]	QuitGuide
EMA[b]	✓	✓ (add-on for this study)
Set a quit date	Quit date set to 2 weeks after randomization and receipt of the iCO via mail	Quit date set to 2 weeks after randomization and receipt of the iCO via mail
Share quit information on social media		✓
Smoking cessation psychoeducation	✓	✓
Content specific to Black smokers	✓	
NRT[c] tips and use advice	✓	
AS[d] psychoeducation	✓	
On-demand tips and exercises		
Coping with cravings	✓	✓
Coping with mood	✓	✓
Coping with stress	✓	
Inspirational messages	✓	✓
Scheduled tips		✓
Treatment messages tailored to currently present smoking lapse triggers	✓	
Coping toolkit	✓	
Guided relaxation and mindfulness exercises	✓	
Challenging automatic thoughts	✓	
Tips for coping with stress	✓	
Interoceptive exposure	✓	
Resources to help distract participants if they experience elevated distress	✓	
Individualized quit plan		✓
Document smoking triggers		✓
List reasons for quitting		✓
Saving from smoking fewer cigarettes		✓
Creating journal entries		✓

[a]MASP: Mobile Anxiety Sensitivity Program.

[b]EMA: ecological momentary assessment.

[c]NRT: nicotine replacement therapy.

[d]AS: anxiety sensitivity.

MASP Condition

Overview

The updated MASP 2.0 app focuses on general interoceptive stress-related issues and interoceptive stress that may be specific to Black smokers [71]. The MASP 2.0 integrates a standard cognitive behavioral therapy smoking cessation protocol (clinical practice guidelines) [68] with transdiagnostic treatment for AS reduction in a culturally adapted framework. Specifically, the MASP 2.0 provides (1) standard treatment on a schedule, (2) scheduled and cued interoceptive exposure sessions, (3) personalized and tailored messaging after each EMA (before and after quitting), and (4) *on-demand* features (eg, coping toolkit and cognitive restructuring exercises) before and after quitting. Culturally specific elements (eg, education about menthol tobacco products, history of tobacco marketing to Black smokers, concerns about pharmacotherapy, religion and spirituality coping, and the impact of racism and racial discrimination on stress and smoking) are included throughout the MASP 2.0.

Treatment on a Schedule

The MASP 2.0 includes 16 intervention videos of 4 to 6 minutes (adapted from traditional AS reduction treatments [72] and the MASP 1.0 audio files), which are delivered through the MASP 2.0 app over the 6-week intervention period. Notably, Black voice actors (men and women) will present all intervention content. New videos will be offered at the completion of the prequit morning and evening EMAs. Participants will have the option to watch videos immediately or later by clicking the on-demand *Treatment Videos* button (Figure 2). Videos can be watched as many times as desired, and the app records the date, time and location when each video is watched (both initiation and completion).

The brief videos provide psychoeducation on multiple topics, including the relationship between stress and smoking, managing uncomfortable sensations, unhelpful thinking, smoking as a temporary coping mechanism to avoid experiencing negative emotions, thinking flexibly, myths about smoking, coping with others smoking nearby, nicotine withdrawal, the importance of using NRT, stress management, interoceptive exposure techniques, and strategies for cessation and relapse prevention. Culturally tailored content (eg, tobacco industry marketing of menthol cigarettes to Black communities, effects of discrimination on smoking and relapse, concerns about pharmacotherapy, chronic stress and race, and the role of AS in interoceptive stress in Black adults) is infused throughout the brief videos.

Exposure Sessions

Internet-based interoceptive exposure is well-tolerated, acceptable, and effective [73,74]. To target AS, graduated exposure to anxiety- and distress-provoking situations and response prevention is introduced in the MASP videos. These exposure exercises were created for the MASP 1.0 study (ie, overbreathing, straw breathing, running in place, chair spinning, and head rush) [57]. The app reminds participants of the importance of completing the exposure sessions 3 times per day during random EMAs. Participants will be instructed to click the *Stress Management Trainings* button to initiate an interoceptive exposure session (Figure 2). The MASP app randomly selects 1 of the 5 exercises each time the *Stress Management Trainings* button is pressed. The participants will be guided through interoceptive exposures by explaining the purpose of the activity and how to perform it, normalizing the physical symptoms experienced during the exercise and relating this experience to the process of quitting smoking (eg, tolerance of physical symptoms related to anxiety, discrimination, and withdrawal). As in the MASP 1.0 pilot [57], when the participant is ready to begin, the app assesses the level of distress (0-100 scale), shows a countdown timer while the exercise is being completed, and assesses the level of distress again (0-100 scale) once the countdown expires. The app suggests repeating the exercise up to 3 additional times if the current reported distress is >50 on a 1 to 100 scale. This strategy aims to increase habituation to feared sensations. In the MASP pilot study [57], participants accessed the stress management training exercises on 6 of the 13 days that preceded their quit date.

EMAs With Tailored Real-time Treatment Messages

During the 2-week prequit period, a message will be delivered at the end of each EMA (5 per day), which will focus on increasing motivation and provide information about cessation (eg, “Everyone experiences negative emotions, such as stress. These emotions do not last forever, but can lead to relapse. Make a specific plan to cope with such feelings”). During the 4-week postquit intervention period, participants will receive personally tailored messages at the end of each EMA based on their responses to EMA items and their reported likelihood of smoking today (ie, 0%-100%). The type of message (eg, motivational, coping with urges or stress, or coping with other smokers nearby) that is delivered at the end of each EMA is recorded in the database; therefore, we may analyze the effect of messages on targeted smoking lapse triggers and anxiety or depression in future EMAs. Participants will receive general quitting advice when they report a 0% chance of smoking that day during EMAs. In addition, the participants will be instructed to review and practice interoceptive exposure exercises to further normalize the symptoms of anxiety and withdrawal to prevent lapse.

On-Demand Features

On-demand tips and relaxation exercises will be available through buttons on the MASP home screen. The research team developed hundreds of unique messages for Smart-T studies [62,75] to address various lapse risk triggers and reduce repetition. MSB, LG, and MJZ led the modification of Smart-T messages and the development of new, short, tailored treatment messages for this study. Participants will be instructed to click the on-demand *Quit Tips* feature when they want to learn more about NRT or coping with smoking lapse triggers (see Figure 3 for the menu of MASP *Quit Tips*); click the *Coping Toolkit* button when they want to access relaxation or mindfulness videos, app-guided exercises focused on challenging automatic thoughts, tips on ways of coping with stress; and click a *Distract Me* button that links to funny or cute videos (Figure 4 for MASP *Coping Toolkit* options). Each time the *Coping Toolkit* option is pressed, a new message or video is presented.

Figure 3. The Mobile Anxiety Sensitivity Program for Smoking Quit Tips feature.

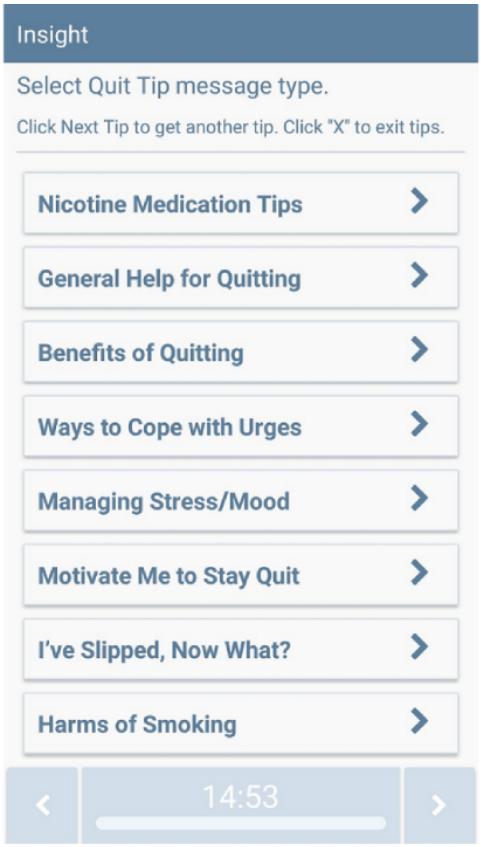
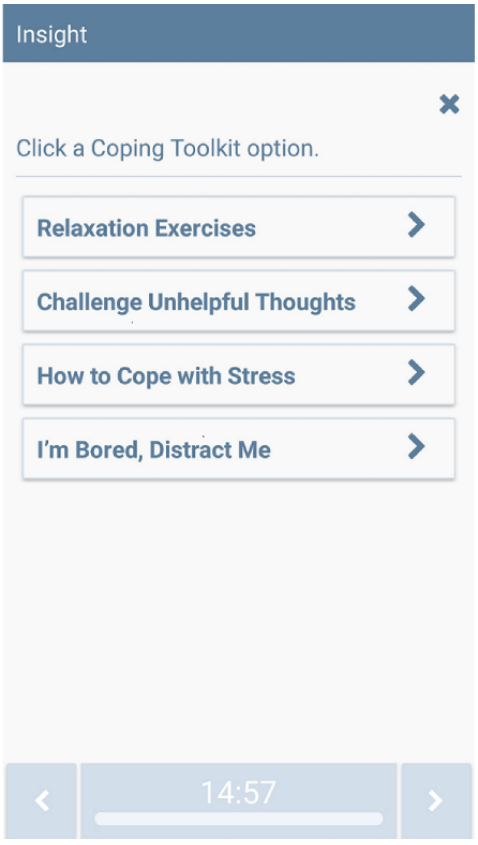


Figure 4. The Mobile Anxiety Sensitivity Program for Smoking Coping Toolkit feature.



MASP 3.0 Development

We will assess the perceived utility of the MASP 2.0 using the standardized System Usability Scale (a participant-completed, reliable, and valid metric for measuring usability and acceptability of technologies) [76-78] and phase 1 qualitative interviews conducted via phone at the end of treatment (week 6). The semistructured qualitative interviews will be conducted by a trained research assistant and audio recorded. These assessments will focus on the ease of interacting with the app, usefulness of app features, how the app can be improved, how sociocultural factors that affect Black smokers could be further woven into the intervention, and the willingness to refer the app to a friend. The refinement process will yield the MASP 3.0. We anticipate that the MASP 3.0 will retain all the key elements of the MASP 2.0 but include improved content that is more culturally tailored based on participant feedback.

Measures

Overview

Baseline and follow-up assessment data will be primarily collected using smartphones through the Insight mobile health (mHealth) platform app software [79]. This approach will reduce data entry errors and the need to retain paper copies of raw data. Each question will appear on the smartphone screen, and the participant will respond by touching their answer on the touch screen. The amount of time needed to complete the questionnaires will vary. The baseline assessment requires up to 30 minutes to complete, and follow-up assessments require up to 15 minutes to complete for both study phases.

Screening

The initial web-based REDCap screening will be completed when the participants click an advertisement for the study. The screener includes an assessment of demographics (eg, sex, age, and race and ethnicity), smoking history, motivation to quit, smartphone and data plan details, and other eligibility criteria. Those that prescreen as eligible via the REDCap screener will be invited to complete a phone call, wherein additional inclusion and exclusion criteria will be assessed. The Rapid Estimate of Adult Literacy in Medicine—Short Form [80] will be used to assess literacy (an English literacy level higher than sixth grade is required to complete the EMAs). Socioeconomic status will be measured as income and the highest level of education. The 6-item Cognitive Impairment Test will be used to assess significant impairment in cognitive function (participants with scores <8 will be excluded) [66]. The Short Scale Anxiety Sensitivity Index is a 5-item measure that will be used to assess AS [64].

Baseline Assessment

The baseline assessment (completed via Insight) includes demographic questions (eg, employment status, income, and insurance), subjective social status [81], Black racial identity [82], acculturation [83], discrimination [84,85], COVID-19 [86], coping [87], attendance at religious services [88], self-rated health [89], health-related quality of life [90], heaviness of smoking [91], tobacco use history, readiness to quit smoking [92], self-efficacy for quitting smoking [93], AS [64], perceived stress [94], chronic pain [95], mindfulness [96], anxiety [97,98], depression [99], social support [100], sleep [101], alcohol use [102], marijuana use [103], and other health behaviors [104].

Follow-up Assessments

Follow-up assessments will be completed using the Insight app at weeks 1, 2 (quit date), 3, 4, 5, 6, 28, and 54 (52 weeks after quitting). Follow-up surveys will be distinguishable from EMAs (ie, participants will self-initiate the assessment by clicking a button labeled *Follow-up Survey* and receive separate compensation for completing these assessments). Importantly, participants will also be asked to complete a phone-based qualitative interview with the study staff at the 6-week follow-up (phase 1 and phase 2). If a participant does not complete the brief app-based follow-up assessments, they will be contacted via call, text, and email to remind them to complete them.

Smoking Outcomes

Biochemically confirmed smoking status will be assessed 3 times per week using the Insight platform (phases 1 and 2). Consistent with most published smoking cessation RCTs (see the Clinical Practice Guidelines) [68] and best practices (see the study by Benowitz et al [105]), our primary study outcome is the biochemically confirmed, 7-day, point prevalence abstinence (PPA) 4 weeks (phase 1) or 52 weeks (phase 2) after the scheduled quit date. Secondary outcomes (eg, time to first lapse and longest time of quitting) will also be examined. Smoking abstinence will be assessed daily via self-report (ie, EMA; weeks 1-6, 28, and 54 [phase 2 only]). The low-cost Bedfont iCOquit smokerlyzer will be used to verify smoking status during the follow-up assessments (ie, quit date; weeks 1-4, 26, and 52 after quitting). Participants will be prompted by the Insight app to connect the iCO device to the smartphone (simply by pushing the power button) and follow step-by-step directions to complete the iCO test. The results of these tests will be automatically date- and time-stamped and saved to our server. We have integrated automated and secure (ie, encrypted) facial recognition software to ensure that only the participants complete the prompted iCO tests. Our CO criteria for abstinence is consistent with numerous studies using cutoffs <7 ppm [106-112]. The half-life of CO is up to 8 hours, depending on a variety of factors (eg, time of day and daily smoking rate) [113]. Expired CO is a valid indicator of smoking status and cessation outcomes and compares favorably with cotinine and other biochemical measures that have longer detection windows [114-116].

EMA and Types

Overview

EMA is currently the most accurate way of measuring phenomena in real time in natural settings [117,118]. EMA items identify fluctuations in key variables that predict study outcomes with less bias than traditional in-person assessments. EMA data will be used to identify moments of high smoking lapse risk, tailor MASP treatment, and identify the treatment mechanisms.

The EMA methodology used in this study is similar to that used in our previous studies and by other researchers [57,62,75,119-126]. EMA items assess multiple constructs

hypothesized to be related to smoking lapse. A total of 3 types of EMAs will be used: daily diaries, random sampling, and event sampling. Random and daily diary EMAs will be prompted and initiated by phone. The phone will audibly and visually cue these EMAs for 30 seconds. If a participant does not respond after 5 prompts, the assessment will be recorded as *missed*. All assessments will be date- and time-stamped for future analyses.

Daily Diary

Daily diary EMAs in the morning will be completed 30 minutes after waking, and daily diaries in the evening will be completed 75 minutes before bedtime. Questions will ask about the previous day and current thoughts, feelings, and behaviors (eg, "How many cigarettes did you smoke yesterday?" and "How many standard drinks of alcohol did you have today?"). Participants will also be asked about smoking cessation medication use and sleep quality for the previous day. Finally, as has been done in our previous work, participants will be prompted to blow into the Bedfont iCO 3 times per week during the evening daily diaries to confirm their self-reported smoking status.

Random Sampling

Participants will be prompted to complete random EMAs scheduled to occur during each participant's normal waking hours 3 times each day (6 weeks total for phase 1 and 8 weeks total for phase 2). Participants will rate their affect by indicating the extent to which they agree or disagree with statements (using a 5-point scale from strongly disagree to strongly agree; eg, "I feel irritable, restless, stressed, alert"). In addition, participants will be asked about current smoking triggers (eg, "I have an urge to smoke" and "I am motivated to AVOID smoking") and indicate current depression (eg, "Rate your current level of depression [feeling sad]") and anxiety (eg, "Rate your current level of anxiety [feeling nervous]"). Participants also will describe their current environment (eg, home and work) and social settings. The other relevant constructs will be assessed during random sampling.

Event Sampling

Participants will be asked to self-initiate smoking assessments (prequit period), lapse assessments (postquit period), and stress assessments (pre and postquit periods) as follows:

1. Smoking Assessments: During the prequit period, participants will be instructed to click a *Record Cigarette* button each time they smoke. Approximately 10% of the time, participants will be asked to answer questions about their affect, stress, and experiences while smoking (eg, "Smoking was pleasurable" and "Smoking improved my mood"). All smoking assessments will be date-, time-, and location-stamped for future analysis.
2. Lapse Assessments: Participants will be instructed to complete lapse assessments (by clicking the *I Am About to Slip or I Already Slipped* buttons) each time they smoke after their quitting date. The lapse assessment items will be nearly identical to those presented in the random and urge assessments. However, questions will be worded to separately assess the participants' responses immediately before and after the lapse. Postlapse assessments will also query about the reinforcing value of the lapse cigarette or cigarettes and the causes of the lapse.
3. Stress Assessments: Participants will be instructed to complete *Report Stress* assessments each time they experience *a significant increase in stress*, and answers to survey questions should be focused on immediate thoughts or feelings. Importantly, MASP prequit EMAs will be followed by predetermined treatment messages, and MASP postquit EMAs will be followed by treatment messages tailored to the participant's responses and current situation. Those assigned to the QuitGuide group will complete EMAs that are identical to the MASP group but will not receive tailored intervention messages.

EMA Alert Settings

During the enrollment call, a phone setup wizard will be used to set participant sleep and wake times for each day of the week (sleep and wake times can be changed for those with variable schedules). This practice reduces the likelihood that the phone will ring when participants are sleeping. In addition, participants may delay EMAs by up to 30 minutes by clicking on the snooze assessment option when an EMA is prompted.

Data Loss Prevention

To overcome the potential loss of data if participants lose their phones (<1% of phones have been lost in most studies), the phones will be programmed to connect to our secure server multiple times each day to upload encrypted data. This will ensure that very little of the collected EMA data are lost. This tactic also allows researchers to remotely monitor each participant's EMA completion rate and call participants when the rate is low. Importantly, EMA data are password protected and encrypted on a study phone. Thus, the study data are only accessible to the research team. If a phone is lost, it will be remotely wiped, and only one replacement phone will be provided to each participant.

The Insight Platform

Overview

The mHealth Shared Resource at the University of Oklahoma Health Sciences Center and Stephenson Cancer Center have developed the Insight mHealth platform, which offers resources that empower researchers to build, test, and launch technology-based assessment and intervention tools [79]. The mHealth resource uses a program manager, 4 project coordinators, and 4.5 computer scientists and engineers who develop and maintain web applications, mobile apps, and relational databases. The applications are developed using state-of-the-art cross-platform design tools.

Smartphone Training

We have developed and repeatedly implemented a brief, user-friendly training protocol for those with limited smartphone experience. Participants will receive training on how to use all features of the MASP app (phases 1 and 2), the EMA-only Insight app (phase 2), and the QuitGuide app (phase 2) during their enrollment phone call and will have access to an *App Instructions* button in the app to remind them about how each

app feature functions (Figure 2). We achieved high EMA compliance rates (eg, 82%-87% of all EMAs completed) using similar protocols in samples of socioeconomically disadvantaged and nondisadvantaged adults [62,75,126,127]. The smartphones will automatically collect intervention delivery data (ie, number of minutes treatment videos are watched and number of times features are used).

Compensation

All participants that enroll in the study will receive a Greenphire Mastercard gift card to facilitate payment for completing study surveys. Greenphire offers an auditable mechanism for all study payments. Participants will receive US $30 for completing the baseline assessment and US $15 for completing follow-up assessments at 1, 2 (quit date), 3, 4, and 5 weeks after the baseline. Participants will receive US $45 for completing the 6-week follow-up, which includes an app-based survey, iCO, and phone-based qualitative interviews. Furthermore, phase 2 participants will receive US $50 for completing the 28- and 54-week follow-up assessments (via Insight) and iCO breath tests. In addition, eligible participants will be compensated for completing the EMAs during their study participation (ie, weeks 1-6, 28, and 54). Specifically, phase 1 and phase 2 participants who complete 50% to 74% of the brief EMAs (5 per day × 7 days=35 weekly EMAs) will receive US $60 or US $80 for 6 or 8 weeks of EMA, those who complete 75% to 89% of assessments will receive US $120 or US $160 for 6 or 8 weeks of EMA, and those who complete ≥90% of their EMAs will receive US $150 or US $200 for 6 or 8 weeks of EMA. Participants can click the *Payment* button on the app home screen at any time for an up-to-the-moment summary of the presented EMAs and current completion rate. Payments for completing EMAs will be loaded onto Greenphire cards following weeks 6 (phases 1 and 2), 26 (phase 2), and 54 (phase 2). Participants will not be compensated for accessing the on-demand app features or for competing treatment components.

Statistical Analyses

Qualitative and quantitative data will be collected in phase 2 and will be used to refine the MASP 2.0 into the MASP 3.0 for testing in phase 2. The feasibility and utility of the MASP 2.0 app will be examined by quantifying the use of the MASP 2.0 features (eg, number of assigned videos that are watched) and evaluating participant opinions about the usefulness and helpfulness of the MASP 2.0 features (eg, automated treatment messages that follow EMAs, interoceptive exposure sessions, and treatment videos). During the end-of-treatment qualitative interviews, we will elicit information on what participants liked about the MASP and QuitGuide apps and how the apps could be improved and identify barriers to app engagement. Semistructured qualitative interviews will be audio recorded and transcribed. A team-based approach will be used to determine the appropriateness of incorporating the suggested changes into the refined phase 2 version of the MASP (MASP 3.0). This approach is consistent with the systematic and reflexive interviewing and reporting methods [128] and will help systematically organize qualitative data to guide the refinement of the MASP 2.0 following phase 1 and before testing in phase 2. In addition, a similar procedure will be followed to organize and address qualitative and quantitative data collected as part of the second phase of the study.

Multiple approaches to modeling changes in abstinence will be used to evaluate our primary hypothesis that the MASP 3.0 will result in higher rates of smoking abstinence relative to the NCI QuitGuide app. We will first use the biochemically verified measure of 7-day PPA, which will be collected via Bedfont iCO at each major assessment, as the primary indicator of abstinence. PPA will be defined as no smoking, not even a puff, in the 7 days before any assessment. We will estimate between-group differences by calculating the odds ratio effect sizes (with 95% CIs) for PPA at each follow-up assessment. We will then conduct a series of conditional latent growth models to examine the impact of treatment conditions on abstinence trajectories. We will use multilevel structural equation models to examine the effects of the MASP 3.0 intervention on the longitudinal course of smoking behaviors, as measured by daily dairy and random sampling EMA data. We will conduct survival analyses using Cox proportional hazard models to assess time to lapse and time to relapse and whether the treatment condition predicts patterns of smoking in survival analysis. Similar modeling procedures will be used to determine the impact of treatment conditions on AS, anxiety symptoms, depression symptoms, stress burden, nicotine withdrawal, and craving and whether improvements in smoking cessation outcomes are mediated by reductions in AS and secondary mechanisms.

Results

The phase 1 smartphone app has been developed (Figures 2-4), and data collection began in January 2022. Phase 2 data collection is expected to begin in July 2022.

Discussion

Principal Findings

This study is the first to culturally tailor a smoking cessation app for Black smokers and the first to incorporate AS intervention components into an automated smoking cessation intervention. We hypothesize that participants will use the MASP app features, report that the intervention is useful and helpful, and report that they would refer a friend to use the app. In addition, we hypothesize that participants randomized to the MASP 3.0 intervention will have greater smoking cessation rates 52 weeks after the scheduled quit date than those assigned to the QuitGuide intervention. Furthermore, this study will advance the understanding of the mechanisms related to smoking relapse. Specifically, we will examine the relationships among self-reported anxiety, depression, avoidance, craving, and withdrawal symptoms as they relate to AS and smoking behavior. A deeper understanding of the mechanisms related to quitting success among Black smokers with AS will improve future interventions by isolating specific targets for the timing and content of intervention messages.

Smartphone interventions have great potential to provide low-cost and scalable treatments for diverse populations. In 2021, overall, 85% of US adults reported owning a smartphone, and ownership is high among minoritized populations (83%

among Black adults), as well as individuals with low socioeconomic status (76% among those earning <US $30,000 per year) [129]. The dynamic nature of AS and related symptoms (eg, anxiety, depression, and withdrawal or craving) makes a mobile intervention ideally suited to addressing risk factors and characteristics that vary from person to person and over time. By providing an automated intervention that tailors treatment content based on psychological and environmental contexts in real time, this study has the potential to provide precision treatment that cannot otherwise be obtained via traditional, in-person therapy. If effective, this type of automated, scalable, and culturally informed smoking cessation app can be easily incorporated into other *real-world* settings to reduce health disparities.

Future Work

Studies are needed to translate and culturally adapt effective in-person cessation interventions into mobile, remotely delivered treatments that have greater cessation and reach potential for historically oppressed and underserved populations, such as Black smokers. Given that past work supports the feasibility of providing smoking cessation care via mobile technology [57,62,63], integrated, mobile AS smoking treatment represents a critical *next step* to addressing tobacco-related health disparities among Black smokers. This study is designed to extend our past AS smoking work and the larger field of smoking–emotional disorder comorbidity by refining (phase 1) and testing a fully automated, culturally tailored, mobile AS smoking cessation intervention for Black smokers in an RCT (phase 2). On the basis of the mechanisms of action observed in this study, future work will focus on refining the intervention to more effectively target key mediators between AS and quitting success. Pending efficacy findings, the MASP intervention will be poised for national dissemination and implementation across health care settings.

Acknowledgments

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Data Availability

The authors will provide deidentified data from this project to interested individuals 1 year after achieving the aims of the project (ie, publication of the main outcome paper). These data will be provided in a digital format with clear labels for all variables. Data will be released directly by the investigators, providing evidence for their institution's institutional review board approval for planned analyses of the data. The authors' team will be available to address any queries.

Conflicts of Interest

MSB is one of the inventors of the Insight mobile health platform and receives royalties related to the use of this platform by investigators external to the University of Oklahoma Health Sciences Center. As MSB is a multiple principal investigator in this study, he did not receive royalties for the use of the platform to create the Mobile Anxiety Sensitivity Program for Smoking app.

Multimedia Appendix 1
Peer review summary statement from the National Institute on Minority Health and Health Disparities Special Emphasis Panel NIMHD Research Centers in Minority Institutions (RCMI) (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 180 KB - resprot_v11i5e38905_app1.pdf]

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Abbreviations

AS: anxiety sensitivity
CO: carbon monoxide
EMA: ecological momentary assessment
MASP: Mobile Anxiety Sensitivity Program for Smoking
mhealth: mobile health
NCI: National Cancer Institute
NRT: nicotine replacement therapy
PPA: point prevalence abstinenceRCT: randomized controlled trial
REDCap: Research Electronic Data Capture

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Protocol

The Impact of Resistance Exercise on Muscle Mass in Glioblastoma in Survivors (RESIST): Protocol for a Randomized Controlled Trial

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Abstract

Background: Glioblastoma is the most common primary brain malignancy in adults, accounting for approximately 48% of all brain tumors. Standard treatment includes radiation and temozolomide chemotherapy. Glioblastomas are highly vascular and can cause vasogenic brain edema and mass effect, which can worsen the neurologic symptoms associated with the disease. The steroid dexamethasone (DEX) is the treatment of choice to reduce vasogenic edema and intracranial pressure associated with glioblastoma. However high-dose DEX or long-term use can result in muscle myopathy in 10%-60% of glioblastoma patients, significantly reducing functional fitness and quality of life (QOL). There is a wealth of evidence to support the use of exercise as an adjuvant therapy to improve functional ability as well as help manage treatment-related symptoms. Specifically, resistance training has been shown to increase muscle mass, strength, and functional fitness in aging adults and several cancer populations. Although studies are limited, research has shown that exercise is safe and feasible in glioblastoma populations. However, it is not clear whether resistance training can be successfully used in glioblastoma to prevent or mitigate steroid-induced muscle myopathy and associated loss of function.

Objective: The primary purpose of this study is to establish whether an individualized circuit-based program will reduce steroid-induced muscle myopathy, as indicated by maintained or improved functional fitness for patients on active treatment and receiving steroids.

Methods: This is a 2-armed, randomized controlled trial with repeated measures. We will recruit 38 adult (≥18 years) patients diagnosed with either primary or secondary glioblastoma who are scheduled to receive standard radiation and concurrent and adjuvant temozolomide chemotherapy postsurgical debulking and received any dose of DEX through the neurooncology clinic and the Nova Scotia Health Cancer Center. Patients will be randomly allocated to a standard of care waitlist control group or standard of care + circuit-based resistance training exercise group. The exercise group will receive a 12-week individualized, group and home-based exercise program. The control group will be advised to maintain an active lifestyle. The primary outcome, muscle myopathy (functional fitness), will be assessed using the Short Physical Performance Battery and hand grip strength.

Secondary outcome measures will include body composition, cardiorespiratory fitness, physical activity, QOL, fatigue, and cognitive function. All measures will be assessed pre- and postintervention. Participant accrual, exercise adherence, and safety will be assessed throughout the study.

Results: This study has been funded by the Canadian Cancer Society Atlantic Cancer Research Grant and the J.D. Irving Limited–Excellence in Cancer Research Fund (grant number 707182). The protocol was approved by the Nova Scotia Health and Acadia University's Research Ethics Boards. Enrollment is anticipated to begin in March 2022.

Conclusions: This study will inform how individualized circuit-based resistance training may improve functional independence and overall QOL of glioblastoma patients.

Trial Registration: ClinicalTrails.gov NCT05116137; https://www.clinicaltrials.gov/ct2/show/NCT05116137

International Registered Report Identifier (IRRID): DERR1-10.2196/37709

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KEYWORDS

glioblastoma; myopathy; resistance exercise; functional fitness; quality of life; intervention; randomized controlled trial

Introduction

Background

Glioblastoma is the most common primary malignant brain tumor in adults [1]. With a median age at diagnosis of 64 years and an incidence rate of approximately 4 per 100,000 people in Canada [2] (4.53/100,000 in Atlantic Canada), glioblastoma is an aggressive tumor with an unfavorable prognosis, making it a significant public health issue [3]. Despite advances in surgical, radiotherapy, and chemotherapeutic approaches, the median survival remains discouraging, ranging from 14 months to 22 months [4].

Glioblastoma, a highly vascular tumor, is known to cause vasogenic brain edema and mass effect, which can worsen underlying neurologic deficits [5,6]. The administration of steroids, most commonly dexamethasone (DEX), is a well-established standard of care in the treatment of vasogenic edema and increased intracranial pressure associated with central nervous system tumors [7]. Steroids are often started in the preoperative setting and continued for varying lengths of time depending on the degree of surgical debulking and response to subsequent treatment. In clinical trials, between 40% and 70% of patients require steroids at the start of radiochemotherapy [8,9]. Although DEX has become the mainstay in the management of tumor-related edema, high doses and long-term use can result in a multitude of harmful side effects, including but not limited to myopathy (muscle weakness) [10,11].

About 10% of glioblastoma patients will develop clinically significant steroid-induced myopathy after just 2 weeks of high-dose therapy [12]. With long-term steroid use, as many as 50% to 60% of patients will suffer from myopathy [13]. This risk is further compounded by the age of the patient, as older adults are at higher risk of myopathy given their lower baseline muscle mass [10,13,14]. In conjunction with fatigue and inactivity [13,14], steroid-induced myopathy results in progressive muscle weakness and functional decline. This can cause balance problems, increase the risk of falls and fractures, and make it more difficult to rise from a chair and climb stairs. These changes can result in a loss of independence and a reduced quality of life (QOL) [7,14].

In addition to the neurologic and functional deficits caused by the tumor, patients experience an array of complex symptoms including cognitive difficulties, sleep disturbance, seizures, emotional distress, and fatigue [15]. Tumor location, treatment, and supportive medications all contribute to these troubling symptoms, which affect QOL. Although glioblastoma prognosis has been associated with numerous clinical factors (eg, patient age, extent of maximal safe resection), functional impairment has been consistently shown to be a significant predictor of greater symptom burden [16,17] and survival [4,14,18,19]. As an incurable disease, it is important to consider factors such as symptom management, maintaining functional independence, and preserving or improving QOL [14,20]. Of note, the ability to walk and perform physical tasks was noted as one of 3 top priorities for brain tumor patients [7].

Exercise and Cancer

A growing body of evidence demonstrates that exercise is associated with improved symptom management, physical and mental well-being, QOL, and survival [21-23]. As with any exercise intervention, adverse events can and do occur; however, safety studies have demonstrated that tailored exercise interventions (adapted to disease, treatment, and patient characteristics) are safe both during and post cancer treatment [21,22] The strength of the evidence has led to the development of cancer-specific exercise guidelines advising that all cancer patients should avoid inactivity [23,24]. Notwithstanding, the bulk of the existing literature is limited to the most common cancers and in patients with early-stage disease [23].

Glioblastoma patients are a heterogenous group with complex health care needs, and exercise interventions are often assumed unfeasible or even contraindicated. As such, glioblastoma patients are underrepresented in the exercise oncology literature [25]. Notwithstanding, animal studies have shown that exercise in mice with glioblastoma can delay motor dysfunction. In humans with brain cancer, preliminary data suggest that exercise is safe, feasible, and likely beneficial. Specifically, improvements in symptom severity, body composition, activity levels, aerobic capacity, neurocognitive functioning, headaches, mental health, and QOL have been reported [26,27]. Clinically meaningful changes have also been reported for lower body strength, balance, fatigue, and sleep following exercise [26,27].

A study by Ruden and colleagues [28] found that exercise in adults with recurrent glioma was an independent predictor of survival.

Resistance Exercise

Even with the high incidence of steroid-induced myopathy in glioblastoma patients, few studies have explored the impact of resistance-based exercise on functional status and patient-reported outcomes in this population. Notwithstanding, there is a growing body of evidence that resistance training can mitigate or prevent progressive loss of muscle mass and strength (ie, steroid-induced myopathy or secondary sarcopenia). In this proposal, sarcopenia and myopathy are used interchangeably. Sarcopenia denotes a syndrome characterized by a progressive loss of muscle mass and strength, leading to physical dysfunction, reduced QOL, and risk of death. For glioblastoma patients, sarcopenia can be attributed to both high and prolonged steroid use, reduced activity due to fatigue, deconditioning and functional loss, and advancing age [10,13,14].

Despite the clinical importance of sarcopenia, the management of this disease remains challenging [29]. In general, resistance training is considered a first-line treatment to manage sarcopenia [29,30]. Progressive resistance training using low-to-moderate intensity, weight-bearing exercises has been shown to improve muscle mass, strength, and functional capacity [31-33]. Resistance training has also been shown to improve gait speed and balance and reduce the risk of falls in the elderly [34]. Similarly, resistance training has been demonstrated to be an important element in reversing sarcopenia in cancer patients. For example, resistance training has been shown to reduce body fat and improve muscle mass, strength, functional ability, and QOL in prostate cancer survivors [35-37]. Similarly, resistance training in breast cancer survivors receiving adjuvant chemotherapy has been shown to reverse sarcopenia [38]. Although resistance training has been suggested to be the most important element in managing sarcopenia, others have noted that the additive effects of a combined aerobic and resistance training exercise lead to the greatest improvements in physical functioning [39,40].

We found 3 studies that explored the role of exercise in brain tumor patients; 2 with stable grade II-III gliomas demonstrated that a home-based, remotely supervised exercise program can improve cardiorespiratory fitness and cognitive function [41,42]. Capozzi et al [43] reported that a once-a-week supervised session of combined aerobic and resistance training exercise improved functional performance in grade I-III brain tumor patients. Despite the well-established benefits of both aerobic exercise and resistance training, there remains a hesitancy to prescribe any form of exercise in certain cancer populations, including those with glioblastoma. The concern regarding exercise prescription for glioblastoma is likely the result of the neurological deficits associated with the cancer as well as the lack of clinical trials examining the benefit of exercise in this population [44]. Although safety and feasibility of resistance training have not been widely studied in a glioblastoma population, 3 case studies found that resistance training is safe and feasible for those with glioblastoma [45-47]. Most recently, Halkett et al [48] piloted a tailored exercise intervention for glioblastoma patients scheduled to receive radiation and chemotherapy. Patients participated in a 1-hour combined aerobic-resistance training sessions 3 times a week over the course of 7 weeks of chemotherapy. Sessions were supervised by an exercise physiologist and delivered at the treating hospital. At the conclusion of the trial, patients identified both challenges (ie, managing symptoms, juggling exercise and treatment, difficulties engaging with the program) and benefits (ie, personalized program, improvements in physical and psychological health, regaining a sense of control, interacting with people) associated with participation [48]. In brief, these studies show that glioblastoma patients are willing and able to safely engage in supervised exercise and, in doing so, show improvements in functional performance and QOL. Although promising, these studies are limited to small sample sizes (n=1-19) and nonrandomized designs. The primary purpose of this study will be to examine the impact of a tailored, circuit-based resistance training program on functional fitness for glioblastoma patients on active treatment. Secondary outcomes will include safety, exercise adherence, body composition, cardiopulmonary function, activity levels, general health, fatigue, cognitive functioning, and QOL.

Methods

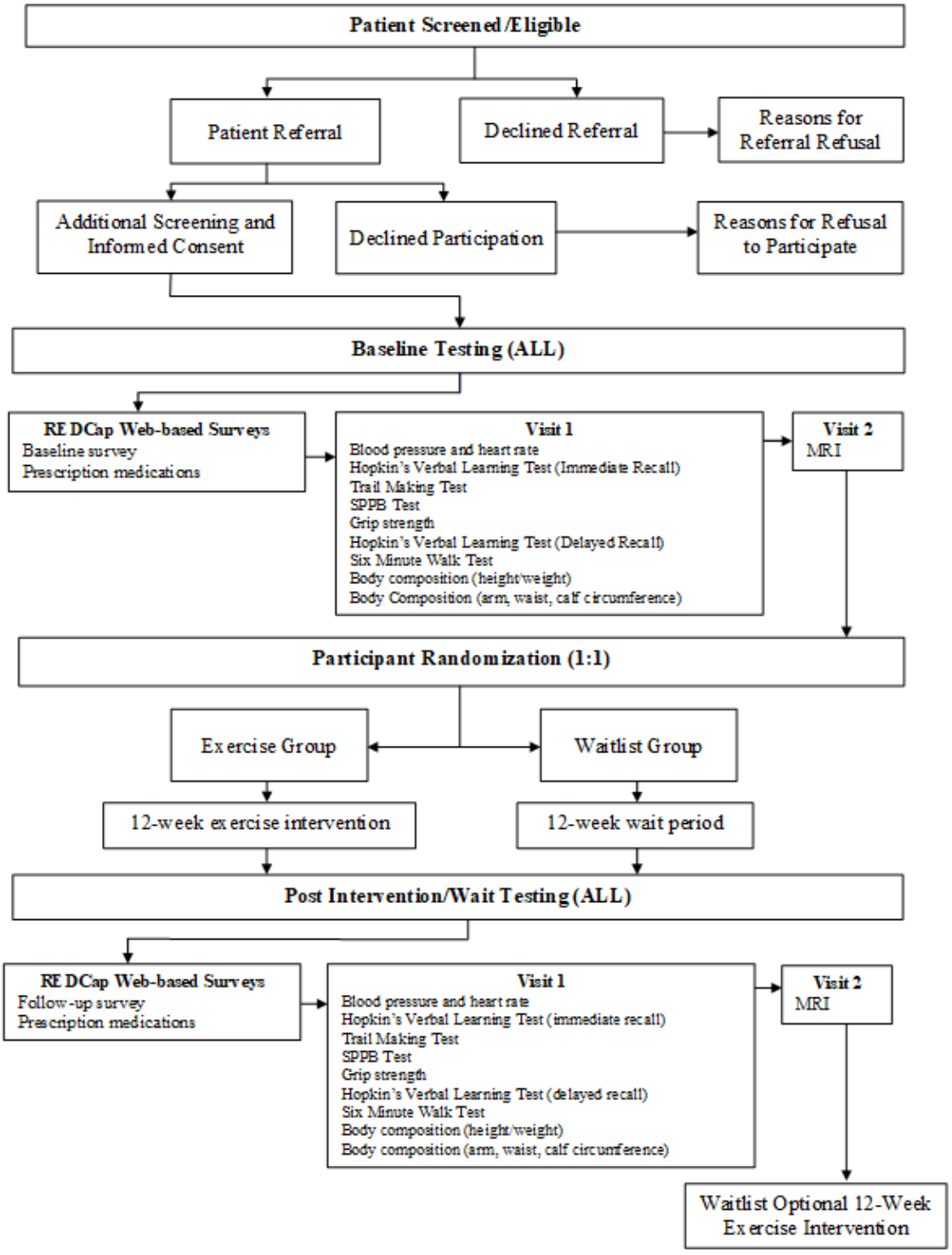
Ethics Approval and Trial Registration

Ethics approval has been obtained from the research ethics boards at Nova Scotia Health (ROMEO REB File number 1027521) and Acadia University (REB File number 22-03).

Study Design and Procedures

This manuscript has been written in accordance with the Standard Protocol Items for Randomized Trials (SPIRIT) 2013 guidelines [49]. This is a 2-armed, randomized controlled trial with repeated measures. Eligible participants will be referred to our exercise lab located at the Nova Scotia Cancer Center, Halifax, Nova Scotia, Canada. Here, they will provide informed consent, complete a baseline survey, and undergo a comprehensive functional fitness assessment conducted by a clinical exercise physiologist (CEP). Following baseline assessments, participants will be randomized 1:1 to either the 12-week exercise intervention (EX) or standard of care, waitlist control group (CON). Block randomization in groups of 4 will be used to ensure an equal balance of participants in each group throughout the study period. The allocation sequence will be concealed from the project coordinator who will be involved in assigning patients to groups. Given the nature of the exercise-based intervention, it not possible to blind participants or the CEPs to group allocation. All participants will return to the exercise lab at the end of the 12-week study to complete a final assessment (Figure 1).

Figure 1. Participant flow.



Participants

We will seek to recruit 38 adult (≥18 years) patients diagnosed with either primary or secondary glioblastoma who are scheduled to receive standard radiation (>65 years old, 3 weeks; <65 years old, 6 weeks) and concurrent and adjuvant temozolomide chemotherapy postsurgical debulking or biopsy. Patients will be recruited through the neurooncology clinic at the Nova Scotia Health Cancer Center. Participants will be screened by MVM and deemed eligible based on the following criteria: (1) histologically confirmed diagnosis of either primary or secondary glioblastoma, (2) received any dose of DEX, (3) Karnofsky Performance Status (KPS) >70, (4) English fluency, (5) physician approval, and (6) willingness to travel to Halifax to participate. Exclusion criteria include (1) unstable or symptomatic cardiac or pulmonary disease, injury, or comorbid disease that precludes ability to safely exercise; (2) significant cognitive limitations or lacking sufficient mental capacity to

give consent (eg, mental health conditions such as schizophrenia, dementia, and brain injury); and (3) uncontrolled seizures associated with impaired awareness. Capacity to provide consent will be assessed through a verification of comprehension through several embedded questions in the informed consent. These questions will ascertain a patient's ability to understand what is being asked of them as a potential research participant.

Standard of Care

Standard treatment for glioblastoma after biopsy or surgical debulking involves a combination of daily oral temozolomide chemotherapy given with daily radiation (5 days/week) for 3 weeks to 6 weeks for a final radiation dose of 40-60 Gy given in 15-30 fractions, respectively. Generally, patients <65 years old receive 6 weeks of radiation with daily temozolomide. Due to poor tolerance of this high dose, patients >65 years old, or those with aggressively growing tumors, receive the same general regime but for 3 weeks. For those between the ages of 65 years and 70 years, 3 weeks or 6 weeks of radiation is chosen based on underlying fitness. Radiation can only be given at the cancer center, so patients attend appointments in person each day. It is during this time that patients may have their steroid dose increased to control the edema associated with radiation. Once radiation is completed, there is a 1-month recovery period, during which there is further adjustment of steroid dose, as needed. Stable patients will continue temozolomide on its own, where it is taken for 5 days a month for 6 months. Throughout this time, patients are examined monthly and monitored every 2 months with magnetic resonance imaging (MRI) of the brain to assess tumor response and guide requirements for further steroid adjustment.

All study patients will receive standard of care treatment. Participants allocated to the CON group will be advised to maintain an active lifestyle but will not receive any formal exercise prescription. CON participants will be given the opportunity to participate in the same intervention following the 12-week control period.

Intervention and Study Setting

Following baseline assessments, participants allocated to the EX group will meet with a CEP at our hospital-based exercise lab. Here, participants will receive an individually tailored, circuit-based resistance training program. Circuit-based resistance training is a common training method used to foster aerobic fitness, muscular endurance, and strength, as well as neuromuscular adaptations in 1 workout. Circuit-based resistance training is comprised of several sets of different exercises with little rest in between each set [50]. EX participants will be asked to return to the lab for 3 to 4 supervised sessions per week for 12 weeks. Sessions will be designed to coincide with standard of care visits to reduce participant burden.

Participants will begin with a light-to-moderate-intensity (3-6 on the 10-point Borg Scale), systematically progressed, circuit-based resistance training program for 20 minutes to 30 minutes per session. Each session will consist of 3 circuits. Each circuit will involve 3 sets of 3 different exercises (20-second intervals for a total of 1 minute per set; short rest between exercises will be provided as needed). Each set will be followed by a 1-minute break. Figures 2 and 3 describe a sample training program and progression. Following the first 3 weeks to 6 weeks of supervised exercise sessions (coinciding with treatment protocol), participants allocated to the EX group will be asked to attend a minimum of 1 in-person session per week for the remaining 6 weeks to 9 weeks of the 12-week program. To reduce participant burden, participants will be offered the option of completing the remaining 2 to 3 weekly exercise sessions at home (supported virtually as needed or preferred). For those living in the Western zone, following the first 3 weeks to 6 weeks of the program, delivered at our hospital-based exercise lab, in-person programming will also be offered at our partner site in Wolfville, Nova Scotia (Acadia University) under the supervision of a CEP. Participants will have the option of completing more than one or all weekly exercise sessions in person at either site. Initial exercise prescriptions will be developed and modified as needed by a CEP in accordance with the participant's health and fitness status. Physician referral, individually tailored, and short, lighter intensity resistance training sessions have been designed to foster program adoption and adherence [51].

Figure 2. Introductory resistance-based exercise circuit (whole body).

Day 1		
Warm up 3 minutes		
Circuit A	Circuit B	Circuit C
20 second on 10s off (as needed), 3 rounds 60s between rounds	20 second on 10s off, (as needed) 3 rounds 60s between rounds	20 second on 10s off (as needed), 3 rounds 60s between rounds
A1. Lower	A1. Lower	A1. Lower
A2. Upper	A2. Upper	A2. Upper
A3. Ant core	A3. Lat core	A3. Rotational core
Cool Down 3 minutes		
Day 2 repeat 1		
Day 3 repeat 1		
Weeks 5-8 new challenging exercises		

Figure 3. Intermediate and advanced resistance-based exercise circuit.

Day 1: Upper + Core		
Warm up 3 minutes		
Circuit A	Circuit B	Circuit C
20 seconds on, 10 seconds off (as needed) 3 rounds 60 seconds between rounds	20 seconds on, 10 seconds off (as needed) 3 rounds 60 seconds between rounds	20 seconds on, 10 seconds off (as needed) 3 rounds 60 seconds between rounds
A1. Horizontal push A2. Horizontal pull A3. Anti-flexion core	B1. Vertical pull B2. Vertical push B3. Anti-extension core	C1. Horizontal pull C2. Vertical push C3. Rotational core
Cool down 3 minutes		
Day 2: Lower + Core		
Warm up 3 minutes		
Circuit A	Circuit B	Circuit C
20 seconds on, 10 seconds off 3 rounds 60 seconds between rounds	20 seconds on, 10 seconds off 3 rounds 60 seconds between rounds	20 seconds on, 10 seconds off 3 rounds 60 seconds between rounds
A1. Knee-dominant bilateral A2. Hip unilateral A3. Rotational core	B1. Hip-dominant bilateral B2. Knee unilateral B3. Dynamic core	C1. Knee-dominant C2. Lower leg C3. Anti-extension core
Cool down: 3 minutes		
Day 3: repeat day 1		
Day 4: repeat day 2		
Weeks 5-8: more challenging movements		
Weeks 9-12: more challenging movements and add in 4th day		

Measures

Sociodemographic Characteristics

Sociodemographic characteristics will include age, sex, gender, level of education, ethnicity, annual household income, and employment status.

Medical History and Performance Status

Medical information will include surgical date and procedure (biopsy/resection), tumor characteristics, treatments received, neurological deficits, treatment-related side effects using the International Common Toxicity Criteria Adverse Event (CTCAE) [52], comorbidities, and prescription medications. Performance status will be evaluated using the KPS [53], assessed by MVM at the time of study enrollment and following the completion of the study.

The primary outcome measure is steroid-induced myopathy as determined by functional performance. Functional performance will be assessed using the Short Physical Performance Battery (SPPB) test [54,55] and handgrip strength [14]. The SPPB uses tasks that mimic activities of daily living and examines 3 areas of lower body function: gait speed, balance, and muscular endurance. Grip strength will be evaluated using a handheld dynamometer. Mean handgrip strength will be calculated from a total of 4 measurements (2 with the right hand and 2 with the left hand) and recorded to the nearest 0.1 kg [56].

Secondary outcome measures will include body composition, aerobic fitness, vital measurements (ie, resting blood pressure and heart rate), physical activity, general health, QOL, fatigue, and cognitive functioning. Participant accrual, attrition, program adherence, reasons for missed sessions, and adverse events will be documented. Body composition measures will include body mass index (kg/m^2), arm circumference, waist circumference, calf circumference [57,58], and muscle mass and quality. Muscle density and intramuscular adipose tissue will be assessed using whole-body MRI [59]. Flex processing will be used to construct muscle, fat, and water images. All scans and imaging processing will be performed using a 3T MRI and associated software at Biotic Imaging for Life. Aerobic fitness will be measured using the 6-minute walk test (6MWT) [60]. The 6MWT is an effective measure of physical functioning in recurrent primary malignant gliomas [61]. General health will be assessed using the EQ-5D-5L [62,63]. The EQ-5D-5L is a valid, widely used tool that measures patient health across 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) [62,63]. QOL will be assessed using the 50-item Functional Assessment of Cancer Therapy-Brain (FACT-Br), which provides scores for physical, functional, emotional, and social and family well-being as well as a brain cancer–specific subscale [64]. Fatigue will be measured using the 13-item Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) [65]. Both the FACT-Br and FACIT-F have been extensively validated and are reliable and widely used tools in the oncology setting [65-67]. Self-reported exercise will be assessed using the Godin Leisure-Time Exercise Questionnaire (GLTEQ) [68-70]. The GLTEQ is a well-validated questionnaire that assesses the frequency and duration of mild, moderate, and vigorous leisure-time exercise participation [70]. Objective physical activity will be captured through a wristworn Garmin activity tracker. Cognitive functioning will be assessed using the Trail Making Test [71] for executive function and the Hopkins Verbal Learning Test-revised for memory [72-74].

Sample Size

Sample size is based on a meaningful change (effect size 0.30) in physical performance [75]. A sample of 24 (12 per group) will allow us to detect differences as small as 0.3 points to 0.8 points on the SPPB with 80% power based on an α=.05 with no sphericity correction. Although randomization should account for variations in sex, we will strive to enroll 38 participants (see the Feasibility section) to explore this covariate.

Feasibility

Our medical oncologist (MVM) typically sees 45 to 50 new glioblastoma patients each year, and roughly half of these patients live outside of Halifax. To increase our reach, we have partnered with JRF (Acadia University, Wolfville) to accommodate patients within the Western zone who may not be able or willing to travel to the main Halifax site. Anticipating a 60%-65% accrual rate, a sample of 12 patients to 13 patients per year is deemed feasible. Should participant accrual be more challenging than anticipated, we will open recruitment to grade III gliomas.

Statistical Analyses

Descriptive statistics will be used to describe the population, accrual, program adherence, and safety. Study outcome measures will be assessed pre- and postintervention and will be analyzed using an intention-to-treat approach. A multiple imputation model will be used to account for any missing data. All participants will then be entered into a mixed effects model with participant group assignment at randomization and time point (pre- and posttest) as fixed factors and participant entered as a random factor. Due to feasibility in recruiting participants in the allotted time, the study will not be fully powered to detect sex-based differences; however, effect sizes associated with the intervention will be calculated and presented for each sex.

Results

This study brings together a multidisciplinary team with extensive expertise in research and clinical practice within the fields of exercise oncology (MRK, SAG); exercise measurement, evaluation, and prescription (MRK, SAG, JRF); exercise physiology (SAG, JRF); behavioral medicine (MRK, CB); medical oncology (MVM); neurosurgery (ACW); research methods and statistics (HFN, CB); clinical trials (all authors); and knowledge translation (all authors). The study team has previously collaborated on research projects including 2 ongoing exercise trials for cancer survivors (Activating Cancer Communities through an Exercise Strategy for Survivors [76], and EXercise for Cancer to Enhance Living well [77]). This study has been funded by the Canadian Cancer Society Atlantic Cancer Research Grant and the J.D. Irving, Limited-Excellence in Cancer Research Fund (grant number 707182). As of March 16, 2022, 1 patient had been enrolled.

Discussion

Overview

Glioblastoma is a devastating diagnosis with a high mortality rate and rapid loss of function and independence; thus, it is imperative to consider factors such as symptom management, maintaining functional independence, and preserving or improving QOL for the duration of the patients' lives. Physical exercise has been well-established to improve functional capacity and QOL in the cancer population. However, few studies have evaluated the efficacy of exercise in mitigating the debilitating physical and functional deficits experienced by glioblastoma patients. Specifically, given the high symptom burden and lack of clinical trials examining the efficacy of exercise in this population, there remains a hesitancy to prescribe any form of exercise. Although the safety and feasibility of exercise for glioblastoma patients have not been widely studied, emerging evidence suggests that brain cancer patients are interested and able to safely engage in physical exercise. Employing a much-needed randomized design, this study will examine the impact of a tailored, circuit-based resistance training program on functional fitness for glioblastoma patients on active treatment. It is anticipated that this study will demonstrate that resistance training not only is safe and feasible for those with glioblastoma but also significantly improves functional status by protecting against steroid-induced myopathy, thereby helping glioblastoma patients maintain their independence, which could lead to marked improvements in QOL.

Dissemination Plan

The proposed work is supported by a multidisciplinary team with the expertise, experience, and infrastructure to ensure the successful implementation of the study. Building on over 13 years of exercise programming for cancer patients and survivors in Nova Scotia, and with the support of the Nova Scotia Health Cancer Care Program, we have built a strong provincial outreach and patient engagement strategy that has provided the necessary foundation for province-wide implementation and dissemination.

Our knowledge translation plan will be directed by 2 main objectives: (1) to raise awareness and understanding of the benefits of physical activity or exercise for glioblastoma patients and their families and (2) to advance the field of study. To address our first objective, following the conclusion of the study, we will create and promote a webinar to share lessons learned with glioblastoma patients and their families. We will also summarize the study findings in a lay document that will be posted on our website [78]. To address objective 2, we will publish our findings in peer-reviewed publications and will present our findings at local, national, and international conferences.

Conclusions

In brief, this study will play a critical role in better understanding how physical exercise can foster an optimal level of function, independence, and QOL in glioblastoma patients.

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This study is funded by Canadian Cancer Society Atlantic Cancer Research Grant and the J.D. Irving, Limited – Excellence in Cancer Research Fund (grant number 707182). The funding organization was not involved in the study design, nor will they be involved in the collection, analysis, interpretation of data, or in writing any resultant manuscripts.

Authors' Contributions

All authors provided substantial contributions to the study protocol. MRK wrote the first draft of the manuscript. CB, JRF, HFN, SAG, MVM, and ACW read, edited, and approved the final manuscript.

Conflicts of Interest

JRF is the Chair of Exercise is Medicine Canada and a shareholder in JackHabbit Inc. The authors have no other conflicts to declare.

Multimedia Appendix 1
Grant agency peer review - reviewer 1.
[PDF File (Adobe PDF File), 4 KB - resprot_v11i5e37709_app1.pdf]

Multimedia Appendix 2
Grant agency peer review - reviewer 2.
[PDF File (Adobe PDF File), 4 KB - resprot_v11i5e37709_app2.pdf]

Multimedia Appendix 3
Grant agency peer review - reviewer 3.
[PDF File (Adobe PDF File), 2 KB - resprot_v11i5e37709_app3.pdf]

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Abbreviations

6MWT: 6-minute walk test
CEP: clinical exercise physiologist
CON: waitlist control group
CTCAE: Common Toxicity Criteria Adverse Event
DEX: dexamethasone
EX: exercise group
FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue
FACT-Br: Functional Assessment of Cancer Therapy-Brain
GLTEQ: Godin Leisure-Time Exercise Questionnaire
KPS: Karnofsky Performance Status
MRI: magnetic resonance imaging
QOL: quality of life
SPIRIT: Standard Protocol Items for Randomized Trials
SPPB: Short Physical Performance Battery

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Protocol

A Skills-Based HIV Serostatus Disclosure Intervention for Sexual Minority Men in South Africa: Protocol for Intervention Adaptation and a Pilot Randomized Controlled Trial

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Abstract

Background: Gay, bisexual, and other men who have sex with men (GBMSM) living with HIV have low antiretroviral treatment adherence in South Africa due to limited skills in managing disclosure and prevention behaviors with sexual and romantic partners. As a result, there is a high HIV transmission risk within HIV-discordant partnerships, but an existing intervention may address these outcomes, if adapted effectively. Healthy Relationships (HR) is a behavioral intervention that was originally delivered in groups and in person over 5 sessions to develop coping skills for managing HIV-related stress and sexually risky situations, enhance decision-making skills for HIV disclosure to partners, and establish and maintain safer sex practices with partners. HR effectively improves prevention behaviors but has yet to be tailored to a non-US context.

Objective: We aim to adapt HR into a new culturally grounded intervention entitled *Speaking Out & Allying Relationships* for GBMSM and then assess its feasibility in Eastern Cape, South Africa.

Methods: The study will have 2 aims. For aim 1—adaptation—we will use a human-centered design approach. Initial intervention tailoring will involve integrating Undetectable=Untransmittable and pre-exposure prophylaxis education, developing intervention content for a videoconference format, and designing role-plays and movies for skill building based on preliminary data. Afterward, interviews and surveys will be administered to GBMSM to assess intervention preferences, and a focus group will be conducted with health care providers and information technology experts to assess the intervention's design. Finally, a usability test will be performed to determine functionality and content understanding. Participants will be GBMSM living with HIV (n=15) who are in a relationship and health care providers and information technology (n=7) experts working in HIV care and programming with this population. For aim 2, we will examine the feasibility of the adapted intervention by using a pilot randomized control design. There will be 60 individuals per arm. Feasibility surveys and interviews will be conducted with the intervention arm, and behavioral and biomedical assessments for relationship and treatment adherence outcomes will be collected for both arms. All participants will be GBMSM living with HIV who are in a relationship with an HIV-negative or unknown status partner.

Results: Intervention adaptation began in August 2021. Initial tailoring and the refining of GBMSM intervention preferences were completed in December 2021. Usability and feasibility assessments are due to be completed by March 2022 and February 2024, respectively.

Conclusions: GBMSM need efficacious interventions that tackle partnership dynamics, HIV prevention, and treatment outcomes for antiretroviral treatment adherence and viral suppression in South Africa. Harnessing everyday technology use for social networking (eg, videoconferences), Undetectable=Untransmittable education, and pre-exposure prophylaxis to update an existing intervention for South African GBMSM has the potential to strengthen relationship communication about HIV treatment and prevention and, in turn, improve outcomes.

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KEYWORDS

gay; bisexual; men who have sex with men; HIV intervention adaptation; videoconference delivery; HIV; public health; mobile phone

Introduction

Background

The past 20 years have seen a growth in HIV research and programmatic attention focused toward gay, bisexual, and other men who have sex with men (GBMSM) in Southern Africa. What was long considered a generalized epidemic among heterosexual individuals is now recognized to be paralleled by a devastating epidemic among GBMSM [1]. To date, the recruitment of GBMSM for HIV surveillance and intervention studies has consistently demonstrated high uptake, retention, and acceptability in South Africa [2-5]. Moreover, these studies have reported HIV prevalence rates ranging from 13.2% to 49.5% for GBMSM, but only 10% to 18.6% of these GBMSM are taking antiretroviral treatment (ART) [3,6,7]. Interventions are needed to address this gap, especially if these consider the influence of relationships on HIV treatment outcomes.

South African GBMSM are often not adherent to their ART while in relationships because of poor skills for managing HIV disclosure and prevention with partners [8]. Among GBMSM who have access to ART, 91% are suboptimally adherent, and many do not know that optimal adherence can lead to viral suppression and the elimination of onward transmission (ie, Undetectable=Untransmittable [U=U]) [9-13]. Stigma acts as a significant barrier to ART initiation [14]. Engaging in HIV care and treatment requires men to disclose their serostatus to others, and there is evidence that social isolation and rejection by sexual or romantic partners prevent men from adopting ART [15,16]. As a result, GBMSM often drop out of clinical care after testing HIV positive, and during this time, they do not disclose their HIV status to partners or use condoms and lube, leading to an increased HIV transmission risk [2,17]. Only after developing an AIDS-related illness however do GBMSM start ART, if at all [8,18]. To prevent being involuntarily disclosed as HIV positive to their sexual partners, GBMSM will often skip ART dosages regularly or stop altogether [8,17].

In previous work, Daniels et al [19] demonstrated that GBMSM relationship dynamics encompass inabilities to discuss safe sex and limited serostatus disclosure—dynamics that result in suboptimal ART adherence. Also, in their study, a 1- to 2-year drop-off along the treatment cascade after testing HIV positive was commonly discussed, corresponding with similar findings for GBMSM in Kenya [1,17,20]. At present, GBMSM do not disclose their HIV status to other GBMSM, thereby increasing social isolation [2,15]. Further, it was shown that for each year of age that participants identified as GBMSM, their odds of testing HIV positive increased by 27%, and the coefficient for the number of clinic visits decreased by 14.5% [21]. Another major qualitative theme revealed that GBMSM will stop ART when starting a new relationship or moving in with their boyfriend out of fear of involuntary HIV disclosure, which is similar to findings in other African settings [18,19]. However, after being out of care and developing AIDS-related illnesses, 84% of GBMSM reported that they disclosed their HIV status and sexuality to an immediate family member. Disclosure allowed them to secure support for their HIV treatment, but this HIV disclosure does not extend to partners [21]. Consequently, GBMSM often encounter significant levels of HIV-related stress and exhibit poor coping and disclosure skills.

Addressing partnership dynamics may improve the effectiveness of HIV treatment interventions for GBMSM in South Africa. However, few HIV treatment interventions have been implemented with African GBMSM, and a growing body of global evidence suggests that GBMSM partnership dynamics are fueling HIV transmission such that one-third to two-thirds of new HIV infections among GBMSM occur within serodiscordant partnerships [22-24]. In South Africa, one study found high rates of regular partnerships for GBMSM (70.5%-75.7% of participants), within which HIV infection was significantly associated with reporting a primary male partner [6]. Among a large sample of male couples (N=300), the prevalence of HIV was high (42%), with 33% of men in serodiscordant relationships living in Kwa-Zulu Natal, South Africa [25]. Despite high levels of HIV testing in the past 6 months (65%), condom use with sex partners has been low (8%). Further, GBMSM have reported low levels of willingness to use pre-exposure prophylaxis (PrEP; 16%) [26]. Factors that limit engagement in HIV prevention among partnered men include relationship dynamics (ie, poor communication skills, the misplaced belief that relationships are protective of HIV, and fears of partner rejection) and stigma from health care providers [16,25]. However, these outcomes can be mediated by skill building in partner communication, disclosure, and prevention.

Healthy Relationships (HR) is a behavioral intervention that was originally delivered in groups and in person over 5 sessions. HR aims to (1) develop coping skills for managing HIV-related stress and sexually risky situations, (2) enhance decision-making skills for HIV disclosure to partners, and (3) establish and

maintain safer sex practices with partners. HR integrates edited movie scenes for participants to view and role-plays that model effective communication skills [27]. HR has been used with HIV-positive GBMSM and women in the United States. In the original HR intervention, Kalichman et al [27] recruited 176 participants into the intervention arm, of whom 88% were GBMSM. Those who received the intervention showed a significant decrease in unprotected sex rates and a lower risk of HIV transmission at 6 months. Marhefka et al [28,29] adapted HR into a videoconference format, delivering the entire intervention to women in rural Florida. Participants in the intervention expressed a high satisfaction rate (84%) and had 7 fewer unprotected sex incidents compared to those among the control participants [28-30].

In our study, HR will be adapted and pilot-tested as a videoconference-delivered intervention for HIV-positive GBMSM with partners by using a design process that incorporates local voices to create an intervention that reflects the lived realities of South African GBMSM. This project aims to develop HR for GBMSM in South Africa into a new, culturally adapted intervention entitled *Speaking Out & Allying Relationships* (SOAR). SOAR will be delivered via the internet, with participants joining via smartphone and video chat. HIV treatment interventions delivered via videoconference are feasible, given the expansion of inexpensive smartphone technologies in South Africa; 84% of adults own a smartphone with which they access the internet and engage with social media [31]. Increased evidence shows that GBMSM access web-based social networking sites and use SMS text messages for social networking through mobile and smartphone technologies, creating the potential to tag on ART adherence interventions [32-34].

Web- and group-based HIV interventions are demonstrating feasibility in diverse African settings. SMART Connections is a 5-session ART adherence and retention in care intervention that was delivered to HIV-positive youth in Nigeria through closed, secret Facebook group sessions [35]. Feasibility results showed high engagement, with at least half of the participants engaging in all sessions and providing recommendations for larger groups. In South Africa, a web-based chat room was offered to youth for HIV support between adherence club sessions by using the MXit social network platform (MXit Ltd) [36]. This intervention showed mixed results; 34% of participants used the web-based group at least once, and 84% approved of the group, but there was a loss of interest. This suggested the need for an adaptation that is tailored to youth subgroups. A small-group, video-based HIV prevention intervention delivered over 5 sessions for motivational skill building, when compared to HIV education only for female military personnel in Nigeria, was effective at 3- and 6-month follow-ups [37]. Given this emerging evidence for web-based HIV interventions, adapting an evidence-based intervention into a videoconference format for GBMSM may be feasible and improve their HIV treatment outcomes.

To further support the proposed delivery method of their intervention, Daniels et al [38] found that GBMSM are willing to complete HIV-related group work, as it is empowering for GBMSM to learn that they have shared experiences based on their sexuality and HIV status. GBMSM receptivity supports the group-based design of an intervention. Further, GBMSM are interested in HIV treatment interventions that use mobile health (mHealth) tools, and videoconference modalities offer the opportunity to create the group experience that GBMSM value [39]. Specifically, Daniels et al [39] showed that mHealth interventions are feasible, given that 71% of 20- to 25-year-old GBMSM own a smartphone. In the same study, 83% reported that they would be interested in engaging in a web-based platform for combined HIV and GBMSM support. These basic feasibilities and preferences support our planned technical adaptations and enhancements for SOAR, including a videoconference format.

Herein, we present our protocol for intervention adaptation followed by a pilot randomized controlled study to assess SOAR feasibility for South African GBMSM. The findings from our study will inform a larger clinical trial for determining SOAR effectiveness in improving HIV disclosure, relationship communication, and viral suppression.

Theoretical Framework

SOAR will be guided by social cognitive theory (SCT), which posits that cognition, behavior, and environment interact and influence health outcomes, like HIV risk reduction, disclosure, prevention, and ART adherence [28,40]. The primary focus of SCT is on self-regulation and self-efficacy [41,42]. In SCT, individuals conduct a cognitive process of determining and weighing the costs and benefits of completing expected health behaviors, such as the self-regulation of disclosure stress, that are enhanced by supportive environments (ie, intervention sessions and check-ins via videoconference) [29,42]. The intervention is expected to enhance skills for coping with HIV-related stress and build skills for the self-regulation of disclosure, treatment, and prevention [41]. These are complemented with self-efficacy, which is the ability to be motivated and have confidence in healthy behaviors and communication in relationships [43]. Within the SCT model, self-regulation and self-efficacy are facilitated by HIV risk reduction; treatment education, including U=U, HIV prevention (eg, partner referrals for HIV testing), and PrEP education; and skill building for the disclosure of HIV status and sexuality in a confidential group environment [41,43]. The ability of GBMSM to plan for safe sex and consider HIV disclosure to partners through the intervention will support ART adherence and engender a sense of agency, thus reducing the negative feelings related to their HIV status and internalized HIV stigma [2,33].

Methods

Ethics Approval

Our study has been reviewed and approved by the University of Cape Town Review Board (approval number: FWA00001938) with reliance by the institutional review boards at Arizona State University (approval number: STUDY00014539) and the University of Michigan (approval number: HUM00208997).

Study Design Overview

The study will involve intervention adaptation (aim 1) followed by a randomized controlled trial (aim 2) to assess feasibility. For adaptation, we will use a human-centered design (HCD) approach. HCD is a multistep approach to gathering different perspectives and experiences from key stakeholders (GBMSM and health care and information technology [IT] specialists) and end users (GBMSM in relationships) for iterative intervention adaptation to include technology integration in context for implementation [44]. Furthermore, our HCD approach will involve initial tailoring based on preliminary research and the refining of GBMSM intervention preferences, followed by the determination of usability. Finally, a feasibility study will be conducted by using a randomized control trial design with GBMSM in relationships. Although the study will not be powered to detect behavioral changes resulting from the intervention, the findings will provide a baseline to determine the intervention effect for the subsequent clinical trial.

Aim 1 Study Procedures for the Adaptation of HR Into SOAR

Initial Tailoring

HR tailoring will be completed by the research staff to include the integration of U=U and PrEP education and messaging, and based on preliminary research, contextually relevant movie segments and role-plays for coping and risk assessment skill building will be developed. Additional intervention components that will be developed include a partner referral letter for HIV testing, action plans, and a monthly videoconference group check-in. The partner referral letter will provide access to HIV testing, U=U and PrEP education, and related local services that are available in the area and be designed to be provided by the participants, who will self-report delivery only [45]. The objective of the letter is to serve as 1 of 2 measures of partner engagement in HIV prevention and care [46]. Action plans are the second measure, and they will be designed such that GBMSM can devise a plan for coping and deciding whether to disclose their HIV status to their partners. Action plans will be discussed during the monthly group check-in after the five core group sessions are completed.

Refining GBMSM Intervention Preferences

We will conduct 15 individual interviews with GBMSM and 2 focus group discussions with a total of 12 health care providers, program leaders, and IT experts. Interviews will be conducted with GBMSM to assess their experiences with and preferences for disclosure and their interests in and considerations for participating in an intervention that builds HIV disclosure skills and is delivered via videoconferences in a group setting. Additionally, by using the findings from the interviews, a study-specific survey will be developed to refine GBMSM participants' preferences for the intervention. Afterward, focus groups will be conducted with health care providers, program leaders, and IT specialists who provide HIV care or manage GBMSM programming in Eastern Cape and on the internet. The focus group discussions will involve a presentation of the initially tailored HR from the initial tailoring phase, and we will seek feedback on session content based on their experiences with working with GBMSM in this setting. The findings from interviews, focus groups, and study-specific surveys will be integrated into the intervention and then assessed for usability.

Usability

The intervention will be pretested for usability over a 5-week period in 2-hour sessions (1 session per week). A group check-in will then be conducted 3 weeks after participants' last session (week 8). A group of participants (n=7) will complete all 5 sessions together on Zoom (Zoom Video Communications Inc). During the last session, participants will be informed of the date and time for the group check-in session. During the pretest, the interventionist will monitor participants' engagement and follow up with participants who miss a session. Before beginning the pretest, each participant will provide their mobile number to receive group session reminders. All intervention sessions and group check-ins will be video recorded for analysis. All participants will receive a data plan to complete this task.

After the pretest, interviews will be conducted with GBMSM participants, and a focus group will be conducted with health care and IT experts. The interviews with GBMSM participants will cover the following six intervention usability domains [47]: (1) the functionality of sessions with group check-ins, (2) the timeliness and appropriateness of sessions, (3) the clarity of session content delivery, (4) the clarity and management of self-assessments and action plans, (5) incomplete sessions, and (6) the technical transition between sessions and between sessions and group check-ins. The focus group with health experts will involve a presentation of the intervention data that are collected from the pretest. This presentation will include a video recording of 1 session, interview results, and technical challenges. Health experts will be asked to provide their perspective on how these pretest findings will influence the pilot intervention and what corrections are needed to limit the number of incomplete group sessions and technical challenges, in order to improve usability. The findings will be integrated into the final intervention and named *SOAR* for the pilot test in the randomized controlled trial (aim 2).

Aim 1 Participants

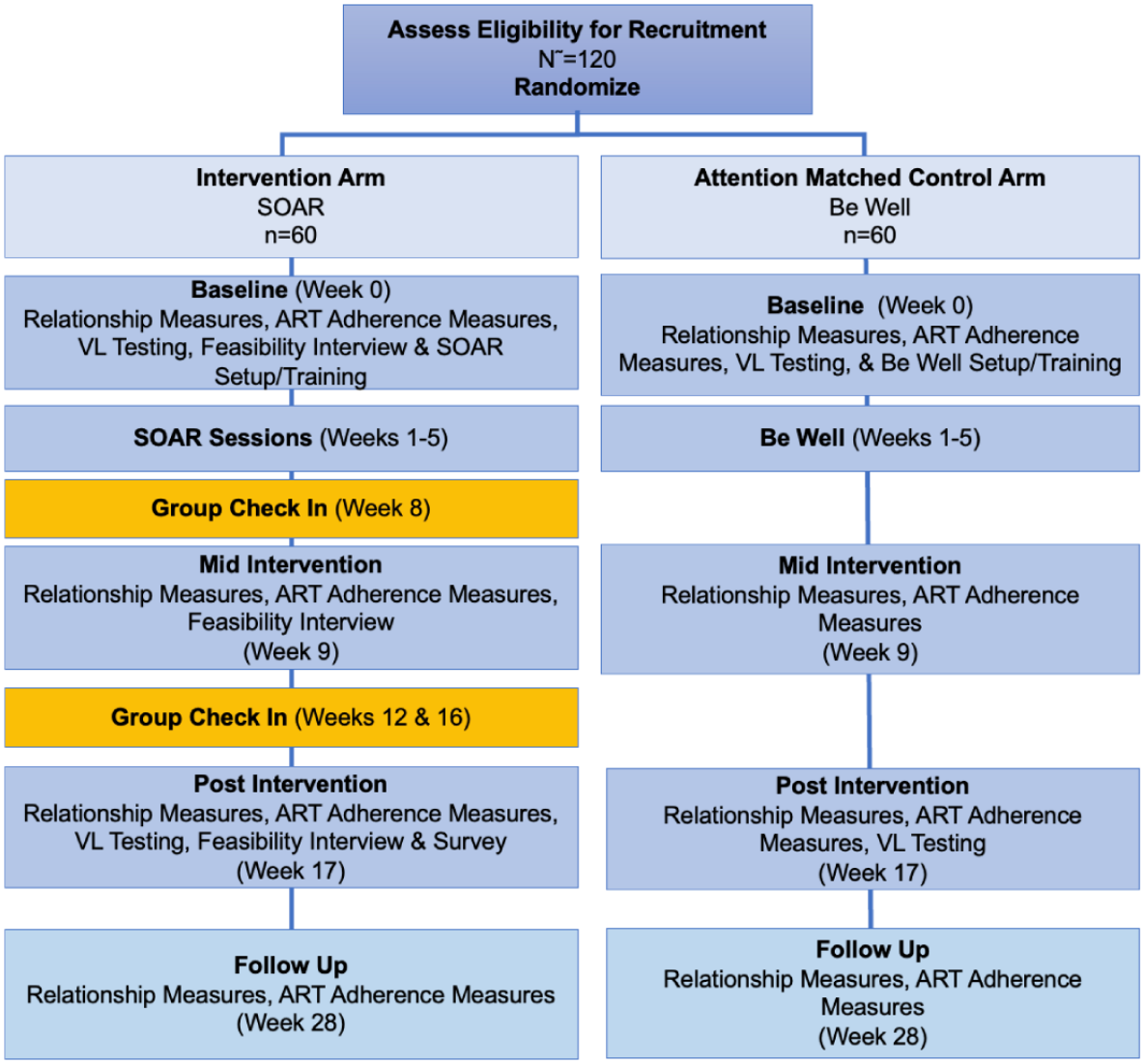
There will be 15 HIV-positive, partnered GBMSM recruited from HIV outreach activities that are led by a local collaborating organization. Further, 12 health care providers, program managers, and IT experts who work in GBMSM programming in Eastern Cape will be purposely recruited. For the usability test, there will be 7 GBMSM participants recruited from the initial 15, and all 12 health care providers, program managers, and IT experts will be recruited. All participants will complete written informed consent and will receive R150 (around US $10) as a travel reimbursement for completing the study activities and a R150 (around US $10) data plan to support their session attendance.

Aim 2 Study Procedures for the Feasibility Assessment of SOAR

SOAR will be assessed by conducting a pilot randomized controlled trial that includes an attention-matched control arm (Figure 1) [40]. Participants will be followed for 28 weeks

(baseline, group sessions [weeks 1-5], group check-ins [weeks 8-16], and follow-up [at 28 weeks]).

Figure 1. Speaking Out & Allying Relationships (SOAR) Intervention Design for Feasibility Pilot-Testing. ART: antiretroviral treatment; VL: viral load.



Intervention Arm Procedures

Group Sessions

Participants will receive the intervention for 5 weeks in 2-hour sessions (1 session per week). Participants will complete the session with the same group of GBMSM. After providing consent, participants will complete Zoom training, which will include a simulated conversation with the interventionist, who will use Zoom in the same room as the participants. Then, each participant's smartphone will be assessed and set up for compatibility for Zoom. Participants will be notified that they will receive an SMS text message reminder 12 hours before each session. At 1 hour before a session, participants will receive an SMS text message with the Zoom link for that session. Participants will complete several self-assessments and develop an action plan during the intervention. Participants will be provided with the partner referral letters via SMS text messaging (REDCap [Research Electronic Data Capture]; Vanderbilt University) or in paper form (their choice) at the start of the study; multiple copies of the referral letters may be requested throughout the study.

Group Check-ins

During the last intervention session, participants will be reminded that they will complete group check-ins (n=3) via Zoom. The dates and times will be provided during the session and then sent via SMS text messages to their mobile phones. Similar to the session procedures, participants will receive an SMS text message reminder 12 hours before a group session and a Zoom link for that session 1 hour before each session.

Attention-Matched Control Procedures

The control arm will maintain their standard of care and receive information that focuses on topic areas like exercise, nutrition, chronic disease, and sexuality. This content will be based on the South African Ministry of Health B-Wise website (B-Wise) [48]. B-Wise is a general healthy living informational website with significant health content. B-Wise and HR are grounded in similar theoretical frameworks that posit that health

information and modeling will empower individuals to make healthy decisions [28,29]. Attention-matched control activities will entail (1) a total of 5 health-related videos that will be sent as Vimeo (Vimeo Inc) web links with passwords via SMS text messaging (1 per week for 5 weeks) and (2) a set of informational-only, 1-way SMS text messages based on B-Wise content (1 per week for 3 months). The videos will correspond with the group sessions, and the 1-way messages will correspond with group check-ins.

Measures

Overview of Measures

Feasibility is the primary outcome for the study, and the secondary outcomes relate to relationship communication, ART adherence, and changes in HIV viral load. Feasibility will be assessed for intervention participants, whereas the secondary outcomes will be assessed for both study arms. Survey measures, interviews, and a biomedical marker of viral load will be used.

Feasibility Surveys

There are 4 domains of feasibility—feasibility [49], acceptability [50], willingness [24], and safety [51]. Feasibility is the ability to recruit participants, retain participants, send and receive messages, and participate in group sessions [49]. Acceptability is the degree to which participants like or dislike components of the intervention [52]. Willingness refers to participants' interest in enrolling in a longer trial and recommending the intervention to others [24]. Safety is the ability to ensure the confidentiality and security of participant data and communication within and outside the intervention [51]. To assess acceptability, the Self-Intervention Evaluation Form and the Client Satisfaction Questionnaire will be administered [53,54]. In addition, a study-specific Likert scale survey will be developed to assess feasibility, willingness, and safety [34]. The study-specific survey will assess participants' perceived ability to send and receive messages and participate in group sessions and group check-ins (feasibility), the likelihood of participants enrolling in a longer study or referring other GBMSM (willingness), the likelihood of participants providing partners a referral letter (willingness), and perceived intervention confidentiality and security (safety).

Feasibility Interviews

In order to understand the feasibility domains, we will conduct 30-minute interviews with purposively selected intervention arm participants (n=30) based on their intervention engagement at baseline, midintervention, and postintervention [55]. Feasibility will be measured by examining participants' attitudes toward various aspects of the intervention, including video-group interactions; referral letters; and perceived changes in the ability to self-manage ART, HIV risk, and HIV disclosure [56]. Acceptability will be evaluated by examining whether participants like or dislike intervention components and the intervention as a whole [56]. Willingness will be assessed by measuring participants' willingness to use the intervention from beginning to end, their willingness to use the intervention in different contexts, and their willingness to suggest the intervention to others [56]. Safety will be examined by measuring participants' perceived levels of discomfort with different components of the intervention and their perceptions of personal safety and unwanted disclosures [51].

Relationship, ART Adherence, and Biomedical Measures

Although our study is not powered to detect changes in these areas, the outcomes from these measures will identify potential directions of effect and inform power calculations for a future efficacy trial. Central to the intervention is creating skills for GBMSM living with HIV to talk to their partners about HIV. The key area—relationship satisfaction—will be assessed by using a 10-item scale that assesses satisfaction with both the partner and the relationship [57]. Communication with partners will be assessed by using the short form (11 items) of the Communications Patterns Questionnaire, which assesses communication and conflict resolution [58]. Disclosure will be measured by using both Kalichman and Nachimson's [59] HIV Disclosure Intent Scale and study-specific questions asking whether the participants disclosed their HIV status to their partners. The questions will also explore participants' partners' reactions, the participant-reported partner uptake of a referral letter, and the reported uptake of HIV testing by a partner. HIV treatment adherence will be assessed by using a visual analog scale [60], and HIV viral load testing will be conducted by using dried blood spots. Relationship and ART adherence measures will be administered from baseline through follow-up, and biomedical measures will be administered at baseline and postintervention to all randomized participants.

Statistical Analysis

Based on our experience from prior studies, we expect around a 23% loss to follow-up, which will result in 92 participants; therefore, we expect to retain 46 participants per group from enrollment through follow-up at 28 weeks. Like other pilot studies, ours is not powered to show the efficacy of the intervention in the study population; the aim of the study is to establish feasibility and the preliminary impact on HIV treatment outcomes before moving to a larger efficacy trial powered for clinical outcomes. We will be able to assess the preliminary impact of SOAR on ART adherence, behavioral measures, and viral load measures. To this end, our sample size (46 participants per group in the randomized controlled trial, yielding data on 92 participants) will yield 70% statistical power with a type 1 error rate at .05 to show a difference between a behavior frequency of 30% in the attention-matched control group and a behavior frequency of 55% in the intervention group for all outcomes.

Aim 2 Participants

All participants will be (1) GBMSM; (2) those aged ≥18 years; (3) those who have been in a relationship for more than 1 month; (4) those who own a smartphone; (5) those who are comfortable with group discussions about HIV; (6) those living with HIV, as determined via confirmatory testing using OraQuick (OraSure Technologies) during screening; (7) those who live in Eastern Cape province; and (8) those who have been prescribed ART but are suboptimally adherent, as measured by a visual analog scale [60]. Participants will self-report (1) being in a relationship with a man (relationships will be defined as a "person you feel romantically or emotionally connected to above all others, and

may be called a partner, boyfriend, lover etc") for more than 1 month, (2) not having disclosed their HIV status to their partners, and (3) having a partner whose HIV status is negative or unknown. All participants will be recruited and screened into the study by the interventionist. Participants will be randomized 1:1 to either the intervention arm (n=60) or the attention-matched control arm (n=60). All participants will complete written informed consent and receive R150 (around US $10) as a reimbursement for attending study visits.

Results

Intervention adaptation began in August 2021, and initial tailoring and the refining of GBMSM intervention preferences were completed in December 2021. Usability and feasibility assessments will be completed by March 2022 and February 2024, respectively.

Discussion

Study Implications

There are poor HIV treatment outcomes for GBMSM in South Africa, given the high HIV prevalence and low ART adherence rates [3,4], which fuel HIV transmission between partners with limited skills in HIV disclosure and communication [2]. To address these outcomes, our adapted SOAR intervention will help GBMSM in South Africa to build skills for coping with HIV-related stress, disclosing one's HIV serostatus and sexuality, and improving communication in relationships. We will assess the intervention's feasibility, its acceptability to participants, its safety, and participants' willingness to use the intervention.

The innovation of the proposed intervention—SOAR—arises from 4 critical, interconnected knowledge gaps. First, it will address the lack of efficacious interventions that address partnership dynamics and, in turn, affect HIV prevention and treatment outcomes for ART adherence and viral suppression among GBMSM in a highly stigmatized, resource-limited setting in South Africa [2,25]. Second, the study will mitigate gaps in the effective adaptation of evidence-based interventions to address the HIV prevention and treatment outcomes of GBMSM who are pursuing relationships in this setting [61]. Toward this goal, GBMSM's preferences for HIV prevention (U=U and PrEP knowledge and partner referrals) and HIV treatment (partner disclosure and ART dose planning) domains will be determined and integrated into the intervention. This approach aims to build GBMSM's self-efficacy in these domains. Further, HCD approaches will be used for adaptation, generating new methods for supporting the increased use of videoconferences for intervention delivery and evidence-based interventions, especially in low-resource communities [47,62]. Third, previous applications of mHealth have focused on SMS text message–delivered HIV prevention and treatment content; aside from the recent work by Essien et al [37] and Henwood et al [36], there are no studies that have harnessed the smartphone capacity of GBMSM in African settings and the commonly used Zoom platform to improve engagement in HIV treatment, which is influenced by relationship dynamics. Finally, our study will address the dearth of HIV research engagement among GBMSM in Eastern Cape province, South Africa, by generating feasibility data to inform a larger clinical trial for measuring the efficacy of the SOAR intervention in effecting viral suppression among GBMSM and improving the referral and uptake of HIV testing and PrEP services among their partners. These are also key to reducing HIV incidence, especially among serodiscordant couples [14,25]. There is a low willingness to use PrEP among partnered GBMSM in South Africa [25], but our partner referral approach may demonstrate feasibility for increasing PrEP uptake among high-risk male couples and may result in the development of PrEP interventions for couples who may be tested in future efficacy trials.

Conclusion

There is an urgent need to develop interventions that provide GBMSM with the behavioral skills for addressing the management of HIV disease while in relationships. If feasible, the proposed intervention has the potential to be implemented in other sub-Saharan African settings with high HIV prevalence rates among GBMSM. Empowering GBMSM to manage their ART adherence and serostatus disclosure while they build a relationship has the potential to be a low-cost and sustainable mechanism for increasing the uptake of HIV care among GBMSM—a group that is currently overlooked in programmatic efforts in sub-Saharan Africa.

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Conflicts of Interest

None declared.

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Abbreviations

ART: antiretroviral treatment
GBMSM: gay, bisexual, and other men who have sex with men
HCD: human-centered design
HR: Healthy Relationships
IT: information technology
mHealth: mobile health
PrEP: pre-exposure prophylaxis
REDCap: Research Electronic Data Capture
SCT: social cognitive theory
SOAR: Speaking Out & Allying Relationships
U=U: Undetectable=Untransmittable

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Protocol

eHealth Interventions Targeting Poor Diet, Alcohol Use, Tobacco Smoking, and Vaping Among Disadvantaged Youth: Protocol for a Systematic Review

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Abstract

Background: Chronic disease burden is higher among disadvantaged populations. Preventing lifestyle risk behaviors such as poor diet, alcohol use, tobacco smoking, and vaping in adolescence is critical for reducing the risk of chronic disease and related harms in adolescence and adulthood. Although eHealth interventions are a promising prevention approach among the general population, it is unclear whether they adequately serve adolescents from disadvantaged backgrounds such as those living in geographically remote or lower socioeconomic areas.

Objective: This is the first systematic review to identify, evaluate, and synthesize evidence for the effectiveness of eHealth interventions targeting adolescents living in geographically remote or lower socioeconomic areas in preventing poor diet, alcohol use, tobacco smoking, and vaping.

Methods: A systematic search will be conducted in 7 electronic databases: the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, PROSPERO, MEDLINE (Ovid), Embase (Ovid), Scopus, and PsycInfo (Ovid). The search will be limited to eHealth-based experimental studies (ie, randomized controlled trials and quasi-experimental studies) targeting diet, alcohol use, tobacco smoking, and vaping among adolescents (aged 10-19 years). Eligible studies will be those reporting on at least one marker of socioeconomic status (eg, social class, household income, parental occupation status, parental education, and family affluence) or geographical remoteness (eg, living in rural, regional, and remote areas, or living outside major metropolitan centers). One reviewer will screen all studies for eligibility, of which 25% will be double-screened. Data will be extracted and summarized in a narrative synthesis. Risk of bias will be assessed using the Cochrane Revised Risk of Bias Tool.

Results: As of December 2021, the title and abstract screening of 3216 articles was completed, and the full-text review was underway. The systematic review is expected to be completed in 2022.

Conclusions: This systematic review will provide an in-depth understanding of effective eHealth interventions targeting poor diet, alcohol use, tobacco smoking, and vaping among adolescents living in geographically remote or lower socioeconomic areas and the factors that contribute to their effectiveness. This in turn will provide critical knowledge to improve future interventions delivered to these populations.

Trial Registration: PROSPERO CRD42021294119; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=294119

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KEYWORDS

eHealth; adolescent; health promotion; diet; alcohol; smoking; vaping; socioeconomic status; remoteness; rural; disadvantage

Introduction

Chronic disease burden is considerably higher among disadvantaged populations such as those living in lower socioeconomic or geographically remote areas [1-6]; therefore, disadvantaged adolescent populations may be vulnerable to experiencing greater chronic disease burden in adulthood than their counterparts. Socioeconomic status is an indicator of an individual's or group's social and economic position within society and is generally associated with access to resources and health outcomes [7]. In Australia, geographically remote refers to areas outside of major cities, classified in order of remoteness and decreasing level of accessibility to services as *inner regional*, *outer regional*, *remote*, or *very remote*. According to estimates from 2017 to 2018, 1 in 5 Australians have multiple chronic conditions, and almost half (45.1%) of those with multimorbidity aged ≥18 years live in the lowest 2 socioeconomic areas, compared to 15.2% in the highest socioeconomic area [8]. Moreover, the prevalence of multimorbidity is greater among populations living in *inner and outer regional* areas than in *major cities* (21% and 18%, respectively). This pattern is not unique to Australia, with similar sociodemographic differences in multimorbidity reported in several other high-income countries [9-14]. Living with a chronic condition impacts an individual's quality of life and is accompanied with social and economic costs; this effect is amplified with multimorbidity [15,16]. Health inequity among disadvantaged populations may partially be explained by a degree of disadvantage pertaining to access to health and support services, as well as education and employment opportunities [17,18]. However, targeting lifestyle differences at a community level to reduce the vulnerabilities of disadvantaged populations [19] may provide positive benefits to overall health and narrow the inequalities in health.

Importantly, many chronic diseases share common lifestyle risk factors that are modifiable, such as poor diet, alcohol use, tobacco smoking, and vaping (electronic cigarette or "e-cigarette" use) [1,20-25]. Thus, reducing or avoiding the engagement in such behaviors can reduce total burden of disease figures. For example, in Australia, 38% of the total burden of disease in 2018 could have been prevented by reducing or avoiding the engagement in modifiable lifestyle behaviors [26]. However, engagement in these behaviors is not uniform across populations, with disparities existing between populations of different socioeconomic positions and between major cities and geographically remote areas. According to the *Australia's Children Report* [27], children and adolescents living in the lowest socioeconomic area compared to those living in the highest socioeconomic area had the following differences: children aged 5-14 years were less likely to meet recommended fruit guidelines (63% compared to 74%) and more likely to consume sugar-sweetened beverages (SSBs) at least once a week (53% compared to 33%); and adolescents aged 12-14 years were more likely to consume alcohol at risky levels (2.2% compared to 0.1%) and be current smokers (2.9% compared to 1.4%). Although not a nationally representative sample, similar sociodemographic differences in diet and alcohol and tobacco use were observed in a recent, large study of 6640 children aged 11-14 years across Australia [28]. Specifically, students of lower socioeconomic status were more likely to use alcohol and tobacco and have poorer diets than students of middle to upper socioeconomic status, and students from regional areas were more likely to use alcohol than students from major cities. Similar sociodemographic differences in diet and alcohol and tobacco use have been reported among adolescents overseas [29-32]. Although vaping has historically been relatively uncommon in Australia, its prevalence has increased over the past decade [33,34]. According to the 2019 National Drug Strategy Household Survey, there has been a significant increase in e-cigarette use among people aged ≥14 years (11.3% in 2019 compared to 8.8% in 2016), with 14.5% of adolescents aged 14-19 years reporting lifetime use of e-cigarettes [33]. Almost half (49.3%) of adolescents aged 14-19 years had never smoked a tobacco cigarette before e-cigarette use. Its use is becoming more common among youth in other countries [35-37], with recent US data from the National Youth Tobacco Survey of 27 million high and middle school students finding that 27.5% (4.1 million) of high school students and 10.5% (1.2 million) of middle school students reported recent use [38]. Moreover, data from the UK Household Longitudinal Study found that e-cigarette use was greater among socioeconomically disadvantaged youth, particularly among never-smokers [39], and the 2018-2019 Kansas Communities That Care Student Survey—a large, cross-sectional, school-based survey of middle and high school students in Kansas (N=132,803)—found that adolescents from rural areas were more likely to report current e-cigarette use than those living in urban areas [40]. A recent meta-analysis of 23 studies found that among people aged <20 years, e-cigarette use triples the risk of initiating tobacco smoking [41]. Although not all individuals who use e-cigarettes will progress to tobacco smoking, they are at risk of experiencing e-cigarette or vaping-associated lung injury [42,43]. Therefore, it is important to consider vaping during adolescence as a chronic disease risk factor.

To reduce the risk of chronic disease in adulthood and address the disproportionately higher rates of chronic disease burden experienced by disadvantaged populations, targeting these behaviors prior to their onset and entrenchment is crucial [44,45]. For a young person, adolescence tends to be a period marked by greater autonomy over their life, as well as increased risk-taking behavior [46-48]. It is a time period in which experimenting with and using alcohol, tobacco smoking, and vaping generally increase [47,49-51]. Moreover, eating habits typically include greater purchasing of fast food away from home [52], along with an increased intake of nutrient-poor food [53], such as discretionary food items (eg, hot chips) [54] and SSBs [55]. These behaviors typically co-occur [56-59] and have been referred to as "consumption behaviors" [60], reflecting that individuals actively consume food, alcohol, or tobacco. In the short-term, these behaviors are linked to detrimental impacts such as poorer quality of life [61], behavioral and mental health issues [62,63], and obesity [64,65]. Several of these behaviors may track into adulthood [66,67], heightening the individual's risk of chronic disease and associated burden over their lifetime, especially when they co-occur [20,68-70]. Altering this trajectory through the engagement of health promoting behaviors

during adolescence shows promise in improving both adolescent and adult health outcomes [71].

Using eHealth interventions (eg, computer-, web-, mobile-, or telephone-based) is an approach with evidence to support its efficacy in targeting multiple risk behaviors in adolescents [72]. Given that eHealth interventions are delivered via the internet, they confer the advantages of increased implementation fidelity, cost-effectiveness, and accessibility, as well as improved student engagement [73,74]. Previous systematic reviews of eHealth interventions targeting at least one of the 4 aforementioned behaviors among adolescents have found them effective in the following areas: improving dietary behavior (eg, eating less unhealthy foods, lowering consumption of total fat and saturated fat, and significantly increasing daily fruit and vegetable intake) [75]; reducing alcohol use [76,77]; and reducing the number of cigarettes and smoking frequency [78]. These reviews, however, focused on adolescents in the general population and did not include vaping as one of the targeted behaviors. It is unclear whether eHealth interventions adequately serve adolescents living in geographically remote or lower socioeconomic areas and are effective in preventing vaping among these populations.

The purpose of this review is to identify, evaluate, and synthesize evidence for the effectiveness of eHealth interventions targeting adolescents (aged 10-19 years) from disadvantaged backgrounds in preventing poor diet, alcohol use, tobacco smoking, and vaping. Considering the personal, social, and economic burden attributed to poor diet, alcohol use, tobacco smoking, and vaping, particularly among disadvantaged populations, this systematic review will contribute valuable insights to the knowledge base and ideally guide the future development of effective eHealth interventions. To our knowledge, this is the first systematic review to focus specifically on eHealth interventions targeting poor diet, alcohol use, tobacco smoking, and vaping among adolescents with lower socioeconomic backgrounds or living in geographically remote areas.

Methods

Guidelines and Registration

This protocol conforms to the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) guidelines [79] (see Multimedia Appendix 1) and was prospectively registered with PROSPERO (CRD42021294119).

Eligibility Criteria

The population, interventions, comparators, and outcomes approach was used to address the research question and eligibility criteria for this review [79].

Population

Eligible studies will be human research studies that target adolescents aged 10-19 years, which aligns with the World Health Organization's definition of "adolescent" [80]. Based on the demographic data presented by authors, studies will be eligible if the sample comprises any of the following: participants with lower socioeconomic status; participants living in rural, regional, or remote areas; and specific sub-group analysis among disadvantaged adolescents. Due to varying methods for measuring and defining socioeconomic status (eg, using the Family Affluence Scale III or Socio-Economic Indexes for Areas scores) and geographical remoteness (eg, based on relative access to services or termed as "countryside," "village," or "remote"), studies will not be limited to using the same measures or definitions; instead, socioeconomic status and geographical remoteness will be based on how they are conceptualized within the studies.

Intervention

Included studies will be those evaluating an eHealth intervention (eg, computer-, web-, mobile-, or telephone-based) targeting at least one consumption behavior—poor diet, alcohol, tobacco smoking, or vaping—among adolescents with lower socioeconomic status or living in geographically remote areas. Interventions addressing other risk behaviors in addition to poor diet, alcohol use, tobacco smoking, and vaping, such as poor sleep, sedentary screen time, and physical inactivity, will be eligible for inclusion as they may help to identify whether targeting a combination of certain behaviors influences outcomes.

Comparators

Eligible studies will compare the experimental group to a control group (eg, no intervention, education as usual, or an alternative intervention) or compare the changes in outcomes over time.

Outcomes

Primary outcomes of interest will include the reduced uptake or use of alcohol, tobacco, and vaping and improved or maintained dietary behaviors. Dietary behaviors will include any dietary outcomes, such as consumption of fruit and vegetables, SSBs, and nutrient-poor foods (junk food). Secondary outcomes of interest will include knowledge about diet, alcohol and tobacco use, alcohol-related harms, future intention to adopt health-related behaviors, motivators and barriers to adopting health-related behaviors, and other health behaviors such as sleep, sedentary screen time, and physical activity.

Studies

Included studies will be randomized controlled trials (including cluster randomized controlled trials) and quasi-experimental studies. They must be published in English and report original empirical findings. No date range restrictions apply for the included studies.

Search Strategy

A database search strategy was developed in consultation with a research librarian. Searches will be conducted in the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, PROSPERO, MEDLINE (Ovid), Embase (Ovid), Scopus, and PsycInfo (Ovid). The searching strategy to be used for all electronic databases is provided in Multimedia Appendices 2-8. Study references will be imported into EndNote software (Clarivate) and duplicates will be removed prior to being uploaded to Covidence software (Covidence) for screening. Grey literature websites and resources (eg, World Health Organization), conference abstracts, the reference lists

of eligible studies, book chapters, and unpublished works (eg, dissertations and theses) will also be searched to identify any additional studies.

Data Extraction and Screening

To balance rigor with the timeliness of the review, all study titles and abstracts will be screened by one reviewer (LE) against eligibility criteria, with a subset (25%) of studies double-screened by a second reviewer (NN, LAG, or KC). This method has been used in several systematic reviews [72,81,82]. Data will be extracted by one reviewer (LE) and reviewed by a second author (NN, LAG, or KC). Using the Template for Intervention Description and Replication [83], 2 authors (LE and NN, LAG, or KC) will independently pilot the standardized data extraction form by extracting 5 studies and then meet to discuss any required modifications to the form to ensure that all relevant data are captured, such as the following:

1. Publication details (study authors, year published) and study details (country, setting, sample size, and design)
2. Participant characteristics (age, gender, and sociodemographic information, including socioeconomic status and geographical remoteness)
3. Intervention characteristics (mode of delivery, duration and frequency of program, underpinning theory, material and components, and targeted risk behavior)
4. Comparison group characteristics
5. Primary and secondary outcomes
6. Measurement tools

The corresponding authors of the published articles will be contacted if additional information that was not reported is required.

Risk of Bias

The risk of bias of the included studies will initially be judged by one independent reviewer (LE) using the Cochrane Revised Risk of Bias Tool [84]. Sources of bias covered in this tool include the following: randomized allocation to groups, allocation concealment, blinding of participants and personnel, blinding outcome, handling of incomplete data, selective reporting, and other biases not covered. A second reviewer (NN, LAG, or KC) will also rate the risk of bias of the included studies, with any inconsistencies resolved through consultation.

Analysis

A narrative analysis will be adopted to synthesize the study findings from the included studies. To begin, one reviewer (LE) will tabulate the following results to compare study components and findings: sample characteristics (eg, location, socioeconomic status, gender, and age); risk behavior targeted; intervention content and components (including duration and delivery method); underpinning theory; and primary and secondary outcome effect sizes. The quality of the body of evidence will be independently rated by 2 reviewers (LE and NN, LAG, or KC) using the Grading of Recommendations Assessment, Development and Evaluation framework [85]. LE will then follow the UK Economic and Social Research Council guidance for narrative synthesis in systematic reviews [86], identify themes and factors, and subsequently, summarize the studies in a narrative synthesis.

Results

As of December 2021, title and abstract screening of 3216 articles was completed, and full-text review was underway. The results will be summarized in a narrative synthesis. The systematic review is expected to be completed and submitted for publication in 2022.

Discussion

Disadvantaged adolescents, such as those with lower socioeconomic status or living in geographically remote areas, may be more vulnerable to experiencing greater chronic disease burden than their counterparts, as evidenced by the disproportionate levels of chronic disease burden among disadvantaged adult populations [1-6]. Consumption-related chronic disease risk behaviors, such as poor diet, alcohol use, tobacco smoking, and vaping, tend to be greater among these populations than their counterparts [27-32,39,40]. In order to reduce this burden, prevention and early intervention is critical. Several systematic reviews have supported the efficacy of universal eHealth interventions in targeting diet and alcohol and tobacco use among adolescents [75-78]; however, it is unclear whether eHealth interventions adequately serve adolescents living in geographically remote or lower socioeconomic areas. In light of this, this review is the first to systematically examine and synthesize evidence on eHealth interventions targeting disadvantaged adolescents (aged 10-19 years) from socioeconomically disadvantaged backgrounds in preventing poor diet, alcohol use, tobacco smoking, and vaping. We expect that literature on eHealth interventions focused on preventing vaping among disadvantaged adolescents may be limited given that its use has only become more common over the past decade, unlike the other behaviors covered in this review. The results from this systematic review will provide valuable knowledge on the important intervention components of effective eHealth interventions and guide the development of tailored eHealth interventions that are better able to prevent and reduce health risk behaviors among these populations. Ultimately, addressing these health risk behaviors to reduce the vulnerabilities of disadvantaged populations [19] has the potential to provide positive benefits to overall health and narrow the inequalities in health. The results from this review will be disseminated through peer-reviewed journals and conferences to help guide future research projects in this area.

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Authors' Contributions

All authors (LE, NN, LAG, and KC) conceived the initial idea for the systematic review. LE drafted the manuscript, and NN, LAG, and KC provided critical insights. All authors contributed to the revision of the manuscript and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist.
[PDF File (Adobe PDF File), 183 KB - resprot_v11i5e35408_app1.pdf]

Multimedia Appendix 2
Cochrane Database of Systematic Reviews (CDSR) search strategy.
[PDF File (Adobe PDF File), 62 KB - resprot_v11i5e35408_app2.pdf]

Multimedia Appendix 3
Cochrane Central Register of Controlled Trials (CENTRAL) search strategy.
[PDF File (Adobe PDF File), 62 KB - resprot_v11i5e35408_app3.pdf]

Multimedia Appendix 4
PROSPERO search strategy.
[PDF File (Adobe PDF File), 8 KB - resprot_v11i5e35408_app4.pdf]

Multimedia Appendix 5
MEDLINE (Ovid) search strategy.
[PDF File (Adobe PDF File), 14 KB - resprot_v11i5e35408_app5.pdf]

Multimedia Appendix 6
Embase (Ovid) search strategy.
[PDF File (Adobe PDF File), 14 KB - resprot_v11i5e35408_app6.pdf]

Multimedia Appendix 7
Scopus search strategy.
[PDF File (Adobe PDF File), 10 KB - resprot_v11i5e35408_app7.pdf]

Multimedia Appendix 8
Psycinfo (Ovid) search strategy.
[PDF File (Adobe PDF File), 14 KB - resprot_v11i5e35408_app8.pdf]

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Abbreviations

PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols
SSB: sugar-sweetened beverage

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Protocol

The Effects of Overweight and Obesity on Obstacle Crossing During Walking: Protocol for a Systematic Review

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Abstract

Background: Overweight and obesity are significant global health concerns that involve deficits in gait and balance that affect daily activities. Although much is reported about the effect of overweight and obesity on gait during unobstructed walking, not much is known about how overweight and obesity could impact gait under more challenging conditions, such as environments with obstacles.

Objective: The aim of this study is to systematically review and synthesize the available data regarding the effects of overweight and obesity on obstacle crossing during walking.

Methods: This review will follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines. PubMed, Web of Science, Scopus, and SPORTDiscus will be systematically searched with no limitations on publication date. Only full-text English-language articles published in a peer-reviewed journal will be included. Included articles must have compared obstacle crossing during walking in individuals with overweight or obesity to individuals of normal body weight. A total of 2 independent reviewers will select the articles and extract the following 4 sets of data: (1) study characteristics, (2) sample description, (3) obstacle crossing task protocol, and (4) main results obtained. If a considerable number of homogeneous papers are included, a meta-analysis will be conducted. A preliminary search was conducted in November 2021.

Results: The results will include the article selection flowchart as well as tables and figures synthesizing the extracted data on the effects of overweight and obesity on obstacle crossing during walking. The preliminary search identified 73 original records, of which 5 articles met the inclusion criteria.

Conclusions: This review will present researchers and clinicians with an overview of published studies that have compared the performance of obstacle crossing for individuals with overweight and obesity to those of normal body weight. Gaining insight into the control strategies adopted by individuals with overweight and obesity is critical for safe and successful obstacle crossing in this population. We therefore believe that our findings could be useful for identifying people at risk of falls and developing and implementing fall prevention programs for individuals with overweight and obesity.

Trial Registration: PROSPERO CRD42021269949; https://tinyurl.com/3yrwccu4

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KEYWORDS

obesity; obstacle crossing; gait; systematic review; overweight; weight; obstacle; walking; balance; fall; risk; prevention; mobility

Introduction

Overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health. According to the US Centers for Disease Control and Prevention, individuals with a BMI between 25 kg/m^2 and 29.9 kg/m^2 are considered overweight, and those with a BMI over 30 kg/m^2 are considered obese. Overweight and obesity have become a major public health issue, and the incidence of the condition is increasing at an alarming rate worldwide [1]. Recent data from the World Health Organization's Global Health Estimates report that the worldwide prevalence of obesity nearly tripled between 1975 and 2016 and that in 2016, 39% of the world's adult population was overweight and 13% was obese [2]. Overweight and obesity are associated with, among other things, impaired postural balance and gait limitations. Interestingly, biomechanical alterations imposed by the additional loading of the locomotor system have been analyzed and reported in recent reviews (eg, [3-5]). For instance, Molina‐Garcia et al [4] recently reported strong evidence that suggests that gait patterns of children and adolescents with overweight and obesity are characterized by greater pelvis transversal plane motion, higher hip internal rotation and flexion, extension and abduction moments and power generation and absorption, greater knee abduction and adduction motion, and higher knee abduction and adduction moments and power generation and absorption compared with normal-weight counterparts. These biomechanical alterations observed in individuals with overweight and obesity during locomotor tasks further have been reported to significantly increase the risk of musculoskeletal disorders, especially in lumbar, hip, and knee regions (see [3,6] for reviews), the risk of injury while performing activities of daily living (ADL), functional limitations (eg, see [6-8] for recent reviews), and the risk of falls and multiple falls (eg, see [9] for a recent systematic review). We can first mention the systematic review and meta-analysis by Backholer et al [7] that demonstrated a graded increase in the risk of ADL limitations from normal weight (BMI 18.5 kg/m^2 to 24.9 kg/m^2) to overweight (BMI 25 kg/m^2 to 29.9 kg/m^2), obesity class I (BMI 30 kg/m^2 to 34.9 kg/m^2), and obesity class II+ (BMI >35 kg/m^2). Additionally, the systematic review and meta-analysis by Neri et al [9] showed that people with obesity over 60 years have a 16% increase in the risk of falls compared to older adults of normal weight.

At this point, however, although much is reported about the deleterious effect of overweight and obesity on gait during unobstructed walking (eg, see [10-16] for recent works published in 2021), not much is known about how overweight and obesity could impact gait under more challenging conditions, such as an environment with obstacles (eg, [12,17-20]). Interestingly, indeed, crossing an obstacle while walking is a challenging task, reflecting a higher risk of loss of balance, trips, and falls [21-26]. Actually, trips over an obstacle are one of the main causes (accounting for up to 53%) of falls during walking in healthy older adults [27]. It has been suggested that these observations could stem from the increased neuromuscular demand of obstacle crossing during walking in comparison to unobstructed walking [23,28,29]. Accordingly, considering the functional limitations imposed by the additional loading of the locomotor system in individuals with overweight or obesity, it is of particular interest to evaluate whether and how overweight and obesity impair obstacle crossing during walking.

To the best of our knowledge, the available evidence on the effect of overweight and obesity on obstacle crossing during walking has not yet been systematically reviewed, and by identifying and synthesizing the current evidence on the topic, we can provide new insights on the potential influence of overweight and obesity on walking in an environment with obstacles. This work was therefore designed to address this issue. Our aim was to conduct a systematic review of published studies that have compared gait parameters related to the performance of the obstacle crossing task in individuals with overweight or obesity and those of normal body weight.

Methods

Guidelines and Registration

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) [30] statement and recommendations and Cochrane Handbook for Systematic Reviews guidelines [31] will be used for this systematic review to identify relevant studies. We will systematically review published studies that have described and compared obstacle crossing during walking in individuals with overweight or obesity and individuals of normal body weight. The protocol for this systematic review has recently been registered in PROSPERO (the International Prospective Register of Systematic Reviews; CRD42021269949).

Eligibility Criteria

Only full-text, peer-reviewed, scientific original articles published in English will be included in this review. Case reports, abstracts, editorials, letters to the editor, case studies, books, chapters, reviews, meta-analyses, and other grey literature materials (government reports, policy statements and conference proceedings, preprints, theses, and dissertations) will be not included. We will use the eligibility criteria below for study selection.

Population

Studies on individuals with overweight or obesity (defined as a BMI ≥25 kg/m^2) may be included. Studies using animal models will be excluded.

Intervention

Studies using the following intervention were considered: obstacle crossing during walking.

Comparator

Studies where individuals with overweight or obesity (defined as BMI ≥25 kg/m^2) and those of normal body weight (BMI 18 kg/m^2 to 24.9 kg/m^2) were compared will be considered.

Outcomes

Studies including spatial-temporal, angular, kinetic, and muscle activation outcomes related to the performance of the obstacle crossing task will be considered.

Data Sources and Search Strategy

A total of 4 electronic databases, PubMed, Web of Science, Scopus, and SPORTDiscus, will be searched systematically from inception onwards to identify studies satisfying the search criteria. The search strategy includes a combination of the following keywords related to (1) the population (individuals with overweight or obesity) and (2) the intervention (obstacle crossing), using the Boolean operators "AND" and "OR" and, if applicable, Medical Subject Headings terms: "obes*" OR "overweight" OR "over - weight" OR "adipos*" OR "body mass index" OR "BMI". The second category specifies the intervention task comprising a term related to obstacle crossing, such as the following: "obstacle crossing" or "obstacle negotiation" or "obstacle avoidance" or "obstructed walking".

Study Selection

A total of 2 independent reviewers (MC and TP) will screen the titles, abstracts, and keywords of each article retrieved from the electronic database searches. Inclusion is based on the previously mentioned selection criteria. The same 2 independent reviewers (MC and TP) will screen the full-text articles for inclusion. A third reviewer (NV) will be consulted in cases of disagreement between the 2 reviewers.

Data Extraction

After completion of the screening process, the same 2 independent reviewers (MC and TP) will extract the following 4 categories of data from each included article: (1) study characteristics, (2) sample description, (3) obstacle crossing task protocol, and (4) main results. Means and standard deviations or medians associated with interquartile ranges or first and third quartiles will be extracted. In the case of missing or erroneous data, the study authors will be contacted for further information. Both independent reviewers will compare the data for consistency. Any disagreement between the 2 independent reviewers will be resolved by consensus or discussion with a third reviewer (NV).

Data Synthesis and Analysis

This systematic review is specifically designed to present an overview of the existing literature on the effect of overweight and obesity on obstacle crossing during walking. We will therefore systematically review published articles that have described and compared spatial-temporal, angular, kinetic, and muscle activation outcomes related to the performance of an obstacle crossing task for individuals with overweight or obesity and those of normal body weight. We will also report the magnitude of the potential differences (as percentages) between individuals with overweight or obesity and those of normal body weight. In the case of a considerable amount of nonheterogeneous studies that meet the eligibility criteria being included, we will verify the possibility of conducting a meta-analysis using specific packages in R (R Foundation for Statistical Computing). The risk of bias of the included studies will be assessed using the Cochrane Collaboration's tool [32] and a specific tool created for a review with a similar scope [33]. Specifically, 2 independent reviewers (MC and TP) will examine the full texts regarding random sequence generation, allocation concealment, blinding of participants and personnel, blinding of the outcome assessment, incomplete data, selective reporting, and other biases (ie, not covered by other criteria). Each criterion will be classified as low-risk (no bias or minimal effects on results), unclear risk (not specified or raises some doubt about the results), and high-risk (may alter the results) [32]. Considering the specific grid created by Galna et al [33], questions will be related to the internal validity, external validity, and reproducibility of the methods related to obstacle crossing. Each question on the quality assessment tool will be scored. A score of 1 will indicate that the study meets the assessment criterion, while a score of 0 will indicate that the assessment criterion is not met. A score of 0.5 will indicate a lack of information or a lack of clarity in the corresponding items. Any disagreement between the 2 reviewers will be resolved by consensus or discussion with a third reviewer (NV).

Ethical Considerations

As this review is limited to publicly available materials, it does not require ethical approval. Results will be shared with the scientific community and the general public.

Results

The search strategy described above was completed in November 2021 and led to 133 records; after removing duplicates, 73 records were identified. After screening titles and abstracts, 5 full texts were reviewed, and all of these articles were included in the review. Data extraction and synthesis are currently ongoing. In line with PRISMA guidelines [30], the number of citations reviewed at each stage of the systematic review will be summarized in a flow chart. The risk of bias of the included studies will be described [32]. Tables and figures summarizing the extracted data will be produced. The dissemination of study results to an international audience through publication in a peer-reviewed journal is expected at the end of 2022.

Discussion

We hypothesize that evidence will show how overweight and obesity negatively affect gait during obstacle crossing. Presumably, individuals with overweight and obesity, due to individual constraints imposed by the obesity on one's gait, would have a higher risk of slips, trips, and falls during obstacle crossing. [27] Obstacle crossing represents an everyday life situation that has been shown to challenge balance and increase the risk of falls [21-26]. Obstacle crossing is therefore an important task to consider in individuals with overweight and obesity [34] and may be useful in identifying those at risk of falls, preventing falls, and reducing the risk of fall-related injuries. However, it is surprising that systematically analyzed data on the effects of overweight and obesity on obstacle crossing during walking are rather scarce. In fact, based on our initial screening process, only a limited number of published articles successfully met all of the eligibility criteria (n=5; [12,17-20]). A total of 2 articles focused on children [17,18], 2 on adults [12,20], and 1 on postmenopausal women [19]. The number of participants with overweight or obesity included in these 5 studies ranged from 12 [17,18] to 54 [20]. Of these studies, 4 [12,17,18,20] assessed the effects of 3 fixed obstacle

heights (low, medium, and high obstacles, measuring from 4 cm to 16 cm in height) on obstacle crossing; 1 study [19] used an obstacle height condition that was based on the length of the participants' lower limbs (30%). The lower-limb kinematics of participants with overweight or obesity and those with a normal BMI as they crossed over obstacles were reported in all studies [12,17-20]; 1 study further collected kinetic data that were time-synchronized with kinematic data [18]. A preliminary and very synthetic analysis tends to show that overweight and obesity impair gait patterns during obstacle crossing in children [17,18], adults [12,20], and postmenopausal women [19].

To the best of our knowledge, this will be the first systematic review to date identifying and synthesizing the available evidence on the effect of overweight and obesity on obstacle crossing during walking. The systematic review was registered in PROSPERO (CRD42021269949). This systematic review will follow the PRISMA statement and recommendations [30] and the Cochrane Handbook for Systematic Reviews guidelines [31] to develop high-quality research questions, capture relevant studies, and critically appraise the relevant studies. A total of 2 independent reviewers will screen titles, abstracts, keywords, and full-text articles and rate the quality of these studies and the risk of bias. A synthesis will then be provided with the information presented in the main text, tables, and figures to summarize the characteristics and main findings of the included studies. On completion, the results of this systematic review will be presented at national and international conferences and submitted for publication in a peer-reviewed scientific journal.

We anticipate that the results of this systematic review will help researchers and health professionals increase the quality of care for people with overweight and obesity. We believe that gaining insight into the mechanisms and strategies adopted by individuals with overweight and obesity is critical for safe and successful obstacle crossing in this population. Along these lines, our findings could be useful for identifying individuals with overweight or obesity at risk of falls and developing and implementing tailored fall prevention programs for these individuals.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

Authors' Contributions

MC, FAB, and NV devised the study scope and research questions and contributed to the study design. MC, FAB, PCRS, NV, and TP wrote and edited the manuscript. MC and TP will review the references and extract data. All authors approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ADL: activities of daily living
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses
PROSPERO: International Prospective Register of Systematic Reviews

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Protocol

Toward More Inclusive Networks and Initiatives in Innovation Ecosystems: Protocol for a Systematic Review

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Abstract

Background: Expanding the cooperation and enlarging the participation of more diverse stakeholders within innovation ecosystems will increase their efficiency and capacity to contribute at local, regional, and national levels.

Objective: This paper presents the protocol for a systematic review that will identify "opening-up" strategies of innovation ecosystems for increasing the participation of more diverse innovation stakeholders, particularly from low-innovation countries, during the ecosystem formation period.

Methods: An algorithmic search in 4 databases (Web of Science, Cochrane Library, Scopus, and Social Science Research Network) will be applied based on the PerSPecTIF (perspective, setting, phenomenon of interest/problem, environment, optional comparison, time/timing, and findings) methodology, the Cochrane guidelines for qualitative evidence synthesis, and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Selection criteria for eligibility include peer-reviewed articles published after December 31, 1999, and containing original data. No restrictions will be placed on the article language and study region, design, or methodology. Methodological strengths and limitations will be assessed using the Critical Appraisal Skills Programme tool. The thematic synthesis method will be adopted, and the GRADE-CERQual tool will be used to assess confidence.

Results: A preliminary search in Web of Science revealed 2758 records. This work is part of the ANGIE project, which was funded by the European Union's Horizon 2020 research and innovation program (grant 952152) in January 2021. We anticipate that the results of this systematic review will be published in spring 2022.

Conclusions: We anticipate that the outcomes of this systematic review will outline the best practices used by initiatives and networks, as well as their impacts on creating larger and more inclusive ecosystems.

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KEYWORDS

stakeholders; investors; best practice; resources; cluster; accelerator; hub; diverse; diversity; innovative; ecosystem; innovation ecosystem; opening-up strategies

Introduction

The "innovation ecosystem" is an umbrella term used to describe the common efforts of different stakeholders to achieve innovation [1,2]. Suppliers provide key parts and technologies that are complemented by products and services provided by a variety of other actors, while customers establish demand and capabilities. In this process of joint value creation, companies

gain a competitive advantage by appreciating the overall value of the products and services delivered to customers [1,3-5]. Themes including cooperation between actors, creation and acquisition of value by organizations, and ecosystem leadership have received increasing interest from both practitioners and scholars [6]. Nevertheless, the activities and processes taking place during the ecosystem genesis and expansion phases have received limited attention and many relevant knowledge gaps remain [7,8]. Therefore, there is an urgent need to increase our understanding regarding the formation of innovation ecosystems at their early stage and the formation of roles within these structures of collaboration [2].

Expanding the cooperation and enlarging the participation of more diverse stakeholders within innovation ecosystems will undoubtedly increase their efficiency and capacity to contribute at local, regional, and national levels [9,10]. It will also allow innovation ecosystems to capitalize on opportunities arising from lower costs, improved expertise, as well as new markets and technologies [11-13]. Nevertheless, this topic has received limited attention to date despite having a significant impact not only on policies aiming to promote the economic welfare of sectors, regions, and countries but also on innovation research and practice. Therefore, it is crucial to identify effective methods of "opening-up" for innovation ecosystems to broaden the participation of innovation stakeholders, particularly from low-innovation countries and during the ecosystem formation period. This period of ecosystem evolution is the most fragile, as described in recent research [2,7,8]. Therefore, external provision of the necessary conditions, resources, and activities during this period will have the highest impact. Opening-up strategies include collaborative innovation strategies; network-, market-, and crowd-based innovation strategies [14,15]; and any other activities aiming to increase the ecosystem's inclusiveness by enlarging the participation of more diverse innovation actors and broadening the participation among different types of stakeholders [16-19].

The aim of this systematic review will be to identify opening-up strategies of innovation ecosystems for increasing the participation of more diverse innovation stakeholders, particularly from low-innovation countries, during the ecosystem formation period. The available evidence on this issue has not been summarized to date to provide a comprehensive understanding of how inclusive innovation ecosystems are formed. The research question expressed via the PerSPecTIF (perspective, setting, phenomenon of interest/problem, environment, optional comparison, time/timing, and findings) statement [20] is presented in Table 1.

Table 1. Question formulation based on the PerSPecTIF (perspective, setting, phenomenon of interest/problem, environment, optional comparison, time/timing, and findings) framework [20] for qualitative evidence syntheses.

Elements	Question formulation
Per	From the perspective of innovation stakeholders
S	Particularly from low-innovation countries
P	What are the strategies for "opening-up"
e	Within innovation ecosystems
(c)	N/A[a]
Ti	Up to and including ecosystem formation
F	In relation to increasing the participation of more diverse innovation stakeholders

[a]Not applicable

Methods

Overview

The planned systematic review will be conducted according to the current Cochrane guidelines for qualitative evidence synthesis [21] and will be reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [22]. The relevant PRISMA 2020 checklist [22] can be found in Multimedia Appendix 1. The review team includes members trained in systematic review methodology. The protocol has been registered in the Open Science Foundation registry. In case any amendments to this protocol are made during the review process, changes and related reasons will be reported in the final article.

We employed the feasible, interesting, novel, ethical, and relevant (FINER) approach [23] to test the applicability of the research question expressed via the PerSPecTIF statement. The outcome of the FINER approach is presented below:

- Feasible: There is an adequate number of studies for inclusion in the systematic review, since a preliminary algorithmic search in the Web of Science database retrieved 2758 records. Also, the technical expertise of the review team, the dedicated time, and the available funding guarantee its successful completion.
- Interesting: The research questions are interesting, as the systematic review is aiming to provide vital information on opening-up strategies of innovation ecosystems to increase the participation of more diverse innovation stakeholders, particularly from low-innovation countries, during the ecosystem formation period. It is crucial to understand these strategies during the genesis of the ecosystem because it is the most fragile during this period of its evolution. Therefore, external provision of the necessary conditions, resources, and activities during this period will have the highest impact.
- Novel: The systematic review will not only confirm previous findings but will also produce new findings for

increasing the participation of more diverse innovation stakeholders to be used for future policies and actions.
- Ethical: There are no ethical concerns regarding the current systematic review process, as it will be entirely based on published evidence accumulation.
- Relevant: The research questions are relevant to current knowledge, practices, and policies pertaining to innovation.

Inclusion Criteria

Studies investigating opening-up strategies of innovation ecosystems for increasing the participation of more diverse innovation stakeholders will be included. We will consider observational studies that provide original data, independently of the design and methodology adopted.

Exclusion Criteria

We will exclude narrative reviews, systematic reviews, perspectives, opinion articles, and other publications that do not include original data.

Years Considered

The selected scientific databases will be searched from January 1, 2000, to present. All searches will be updated prior to submission of the final manuscript, in case the date of the initial search is more than 12 months older than the date of submission [24,25]. New records will be screened and evaluated based on the inclusion and exclusion criteria set above.

Publication Language

We anticipate a large body of the literature on the topic of this systematic review to be in English. No articles will be excluded based on language, but our search will be conducted using English terms. Articles in languages other than the ones spoken by the coauthors of this study (English, Greek, and German) will be translated into English using Google Translate following previous methodologies [26]. If Google Translate does not generate a good translation or if we are in doubt about the translation generated for a non-English manuscript, the paper will be assessed by a native speaker.

Search Strategy

We will perform a keyword algorithmic search in scientific databases that focus on research topics relevant to our research question. These databases are as follows: Web of Science [27], Cochrane Library [28], Scopus [29], and Social Science Research Network [30].

The search algorithm will be built according to the PerSPecTIF statement [20] described in Table 1 and will be adjusted to the environment of each database. An example of translating the PerSPecTIF statement to appropriate indexing terms based on existing guidelines [21] is shown in Table S1 (Multimedia Appendix 2). A preliminary search on the Web of Science database using these search terms revealed a total of 1301 records. The algorithm is also provided in Multimedia Appendix 2.

In the algorithmic searching we will use Booleans (ie, OR, AND, NEXT, etc) and possibly truncations as well as wildcard characters (*, ?). Finally, we will also check the reference lists of the included studies for potential eligible publications that did not appear in the initial search approach. To comply with the Multi Engine Command Instrument Rating (MECIR) requirement and Conduct of Systematic Reviews in Toxicology and Environmental Health Research (COSTER) recommendations regarding the updating of the searches within 12 months prior to publication of a systematic search [24,25], we will rerun all searches shortly before the final analyses, and any further relevant studies identified will be retrieved for inclusion.

The above-mentioned pilot algorithm was judged by the review team as applicable and appropriate to be used in the official searching procedure. As such, 2 members of the review team, GN and EM, independently conducted the official searching in the selected scientific databases (from the date of their inception to October 2021). The search algorithm was “translated” from one database to another so that it is compatible with the corresponding website’s search engine. ADF confirmed no disagreement between the team members GN and EM in applying the algorithms in all 3 databases.

Study Selection

The retrieved studies from the searching procedure will be managed using the Rayyan online platform [31]. Two reviewers (GN and ADF) with previous experience in conducting systematic reviews will independently screen the retrieved publications for eligibility. A third reviewer (EM) will act as a referee and resolve any potential conflicts. Then, all reviewers will share their notes to confirm and finalize the selection of studies. All 3 reviewers will be provided with written instructions on the selection process and will undergo pilot testing of the systematic review selection procedures on a small subset of the records retrieved. The methodology of the selection process is as follows:

1. The first step includes removing duplicated papers that will arise from the searching procedure.
2. The second step includes checking the publications against the eligibility criteria based on titles and abstracts. At this stage, we will exclude records that are not relevant and do not fulfil 1 or more of the inclusion criteria listed above.
3. The third step includes checking the full texts of the remaining publications against the eligibility criteria. This step will result in the final list of the eligible publications.

A PRISMA flow diagram will be created to describe in detail the procedures of searching and selection of publications in this systematic review [22,32]. A full list of the excluded articles will be provided in the final systematic review paper.

Data Extraction

For each eligible publication, an individual data extraction form will be incorporated. Two review team members will independently extract data from the eligible publications and a referee- investigator will make an ultimate decision in case of a disagreement between review team members. A priori pilot data extraction will be used so that the 2 review team members agree on including missing data that were not initially considered or data that do not need to be extracted. Each team member will extract their data in an Excel spreadsheet (Microsoft Corp). In cases where the presented data are unclear in the articles’ full

text, the data extraction review team members will contact the corresponding authors via email to retrieve them.

Assessment of Methodological Strengths and Limitations

According to the existing guidelines [21], we will assess methodological strengths and limitations as a marker of study rigour using the Critical Appraisals Skills Programme (CASP) tool [33]. CASP is a previously published, commonly used, and validated tool to assess methodological strengths and limitations of qualitative studies [21]. Also, it has shown an interrater agreement of >92% [34]. According to the existing guidelines [21], the aim of this assessment will not be to calculate total quality scores but to provide evidence for a discussion on the studies, their "risk to rigour," as well as whether their methodological limitations may have affected the systematic review findings.

Data Synthesis

We will use the thematic synthesis method to produce syntheses that can subsequently be integrated with an intervention review or analysis.

Assessing Confidence

Based on the existing guidelines [21], we will use the GRADE-CERQual tool to assess confidence in the qualitative synthesized findings. This tool evaluates 4 components (relevance, methodological limitations, adequacy, and coherence) to provide an overall assessment of confidence in the synthesized qualitative findings.

Results

As indicated above, a preliminary search in the Web of Science database revealed 2758 records. This confirms that the systematic search procedure will generate adequate information to achieve the objective of this review. This work is part of the ANGIE project, which was funded by the European Union's Horizon 2020 research and innovation program (grant 952152). The ANGIE project was initiated in January 2021. We anticipate that the results of this systematic review will be published in spring 2022.

Discussion

It is anticipated that the outcomes of this systematic review will outline the best practices used by initiatives and networks, as well as their impacts on creating larger and more inclusive ecosystems with a shared, clearly defined purpose. Additionally, this systematic review will shed light on the steps that innovation ecosystems take to implement a solid opening-up strategy, with the goal of enlarging and broadening the participation and commitment of more stakeholders and encouraging collaborative partnering.

Overall, this systematic review aims to uncover the strategies used by previous and existing ecosystems to become inclusive, fostering the participation of stakeholders at all levels of innovation capacity and taking into consideration gender equality and diversity. Even actors who are moderate and modest innovators can be instrumental, particularly in the early phase of an ecosystem formation [9,10]. Therefore, identifying opening-up strategies of innovation ecosystems for increasing the participation of more diverse innovation stakeholders, particularly from low-innovation countries, during the ecosystem formation period will increase the involvement of different stakeholders and maximize an ecosystem's innovation potential.

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Authors' Contributions

All authors contributed equally to drafting, writing, and reviewing this protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist.
[PDF File (Adobe PDF File), 198 KB - resprot_v11i5e34071_app1.pdf]

Multimedia Appendix 2
Describing literature search strategy.
[DOCX File , 34 KB - resprot_v11i5e34071_app2.docx]

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Abbreviations

CASP: Critical Appraisal Skills Programme
COSTER: Conduct of Systematic Reviews in Toxicology and Environmental Health Research
FINER: feasible, interesting, novel, ethical, and relevant
MECIR: Multi Engine Command Instrument Rating
PerSPecTIF: perspective, setting, phenomenon of interest/problem, environment, optional comparison, time/timing, and findings
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

Exploring the Use of Wearable Sensors and Natural Language Processing Technology to Improve Patient-Clinician Communication: Protocol for a Feasibility Study

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Abstract

Background: Effective communication is the bedrock of quality health care, but it continues to be a major problem for patients, family caregivers, health care providers, and organizations. Although progress related to communication skills training for health care providers has been made, clinical practice and research gaps persist, particularly regarding how to best monitor, measure, and evaluate the implementation of communication skills in the actual clinical setting and provide timely feedback about communication effectiveness and quality.

Objective: Our interdisciplinary team of investigators aims to develop, and pilot test, a novel sensing system and associated natural language processing algorithms (CommSense) that can (1) be used on mobile devices, such as smartwatches; (2) reliably capture patient-clinician interactions in a clinical setting; and (3) process these communications to extract key markers of communication effectiveness and quality. The long-term goal of this research is to use CommSense in a variety of health care contexts to provide real-time feedback to end users to improve communication and patient health outcomes.

Methods: This is a 1-year pilot study. During Phase I (Aim 1), we will identify feasible metrics of communication to extract from conversations using CommSense. To achieve this, clinical investigators will conduct a thorough review of the recent health care communication and palliative care literature to develop an evidence-based "ideal and optimal" list of communication metrics. This list will be discussed collaboratively within the study team and consensus will be reached regarding the included items. In Phase II (Aim 2), we will develop the CommSense software by sharing the "ideal and optimal" list of communication metrics with engineering investigators to gauge technical feasibility. CommSense will build upon prior work using an existing Android smartwatch platform (SWear) and will include sensing modules that can collect (1) physiological metrics via embedded sensors to measure markers of stress (eg, heart rate variability), (2) gesture data via embedded accelerometer and gyroscope sensors, and (3) voice and ultimately textual features via the embedded microphone. In Phase III (Aim 3), we will pilot test the ability of CommSense to accurately extract identified communication metrics using simulated clinical scenarios with nurse and physician participants.

Results: Development of the CommSense platform began in November 2021, with participant recruitment expected to begin in summer 2022. We anticipate that preliminary results will be available in fall 2022.

Conclusions: CommSense is poised to make a valuable contribution to communication science, ubiquitous computing technologies, and natural language processing. We are particularly eager to explore the ability of CommSense to support effective virtual and remote health care interactions and reduce disparities related to patient-clinician communication in the context of serious illness.

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KEYWORDS

communication; technology; ubiquitous computing, natural language processing; cancer; palliative care

Introduction

Background

Effective communication is the bedrock of quality health care, but it continues to be a major problem for patients, family caregivers, health care providers, and organizations [1-4].The ramifications of poor health care communication are profound and can include medical errors [5], suboptimal symptom management [6-9], decreased quality of life for patients and caregivers [10], health care provider distress and burnout [11,12], and inappropriate health care service usage [2]. Effective communication is especially critical in the context of oncology and palliative care, when patients and their families are coping with the stressors of advanced illness and difficult symptoms, such as pain that affects up to 60%-90% of people with cancer [13-15]. Even more problematic is the reality that poor communication related to symptom management contributes to disturbing and unethical health disparities. For example, research has shown that patients from underrepresented racial and ethnic groups are significantly more likely to suffer with undertreated pain [16], die in the intensive care unit when it is not their preference [17,18], and generally experience poorer communication about their health care issues and needs [17,19-22].

Although progress related to communication skills training for health care providers has been made, clinical practice and research gaps persist, including the following: (1) whether the effects are sustained over time [23], (2) which communication training programs are most likely to improve patient care outcomes [23], and (3) the lack of a scalable way to monitor, measure, and evaluate the implementation of communication skills in a natural clinical setting and provide real-time feedback about communication effectiveness [2,24-27]. Leaders in the field, including the Strategic Plan from the National Cancer Institute [28], suggest that to advance the science of communication, we must find ways for continuous, scalable, and clinically meaningful measurement methods [25-27,29,30]. Our protocol helps fill this gap by offering a technology that leverages ubiquitous sensing methods, combined with linguistic and paralinguistic feature engineering methods, to create a novel, scalable, and longitudinal framework to measure the impact of communication in the actual clinical setting tied to a relevant patient outcome such as cancer pain.

Computational methods for processing natural (ie, human) language provide novel opportunities to improve outcomes within health care, including patient-clinician communication. For example, advancements in natural language processing (NLP) technology now make granular analysis of written text and human speech more feasible, allowing us to better parse and understand the dynamics of complex interpersonal interactions [31-34]. This work builds upon prior research regarding NLP analysis of palliative care documentation [31,32,35,36] and evaluation of structured communication skills [37,38], and extends prior work using existing and foundational techniques in NLP and machine learning [39] to implement CommSense. Successful achievement of the aims will establish proof of concept that CommSense can identify relevant verbal (and limited nonverbal) communication signals during patient-clinician interactions, extract relevant metrics of communication performance, and ultimately (long term) provide timely and personalized user feedback to track and evaluate communication performance.

In summary, this proposed research is timely, relevant, and addresses an urgent problem in health care, namely how to assess and measure patient-clinician communication. Improving communication related to cancer pain management can have profound positive implications, such as decreasing patient and family caregiver suffering [40-46], reducing health disparities related to pain management and cancer care [16,19,47-51], improving health care provider job satisfaction [10,52], and mitigating trips to the hospital or emergency department due to uncontrolled pain [53-56]. It is important to emphasize that we recognize the multiple and complex dimensions for improving communication, and many different types of patient-clinician interactions. However, for this initial pilot research, we aim to address 1 aspect, specifically health care provider communication related to cancer pain in the palliative care context, and to determine if we can make a positive impact by building technology to measure and evaluate key features of these types of conversations that can be assessed in real time. Given the scope and intent of this pilot work and the documented need related to this problem, we believe it is an appropriate place to start. If successful, we envision that the CommSense platform will be applicable to a broad range of health care–related conversations and contexts.

Preliminary Work

CommSense will build upon an existing Android smartwatch platform (SWear) developed by coauthors (LB and MB) to collect sensor signals from smartwatches [57]. Prior work using SWear has demonstrated acceptance of the technology, accuracy of the underlying NLP technology, and the ability to successfully use the platform across multiple contexts and study samples [58-64]. Specifically, the SWear platform has been previously used to evaluate communication in socially anxious individuals, and the feasibility and ability of Swear to extract audio features (eg, energy, pitch, Mel-frequency cepstral coefficients and NLP features such as sentence representation from pretrained Roberta/Sentence Transformers, term frequency-inverse document frequency) for predicting different anxious states during natural conversations have been established. Although this study addresses a different clinical problem, the foundational and established NLP methods, and the techniques for collecting, storing, and processing audio data are similar. This research leverages our team's complementary skillsets related to smartphone-based biomarkers of cognitive states and virtual human training systems for patients, clinicians, and teachers

(engineering, LB [65-69]); mobile and ubiquitous computing, NLP technology, machine learning (engineering, MB [66]); patient-provider communication and smart health (nursing, VL [70-73]; medicine, TF [74-77]); informatics (medicine, DL [78,79]); and oncology and pain management (nursing, VL [73,80-82]). Our team possesses the clinical and technical expertise necessary to support the aims of this research.

Aims

This is a 1-year (November 2021-November 2022) "proof-of-concept" feasibility study to develop a novel ubiquitous system and associated algorithms for measuring quality of conversations (CommSense) that can (1) be implemented on mobile devices, such as smartwatches; (2) reliably capture patient-clinician interactions in a clinical setting; (3) process communication to extract key markers of communication effectiveness and performance; and (4) ultimately (long term) provide real-time feedback to end users to improve communication and patient health outcomes.

Methods

Specific Aim 1: Establish Feasible Metrics of Communication to Extract From Conversations (Months 1-3)

Data Collection

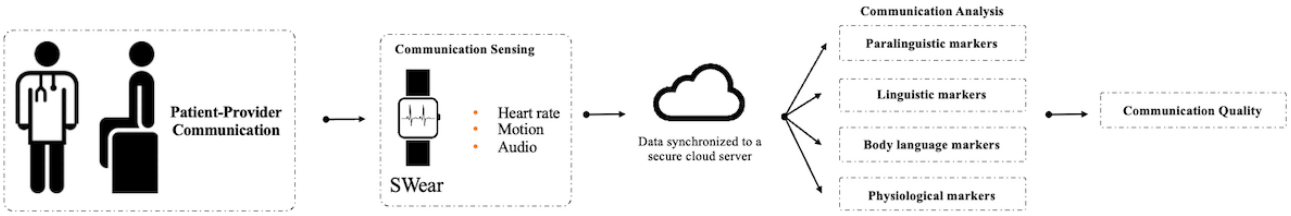
Clinical investigators will conduct a thorough review of the recent health care communication and palliative care literature to develop an evidence-based "ideal and optimal" list of communication metrics. We anticipate that this list will have two categories: (1) general best practices of health care communication (eg, verbal metrics such as the amounts of silence or pauses; speaking turns, interruptions, and overtalking; open-ended versus closed-ended questions; and nonverbal metrics, such as eye contact; arms crossed or open; sitting or standing) and (2) metrics more specific to conversations about cancer pain management (eg, assessment questions related to the severity, onset, and quality of the pain). We will organize this list conceptually around the 6 recommended domains to operationalize patient-centered palliative cancer care communication as detailed by McCormack et al [25,83], including exchanging information, fostering healing relationships, recognizing and responding to emotions, managing uncertainty, making decisions, and enabling patient self-management. We will also organize this list by "need," "nice," and "next" to record CommSense features considered essential by the clinical team, including the preferred and future features. This initial list of communication metrics will encompass the "what" (content questions) and the "how" (in what manner the questions are asked). This list will be discussed collaboratively within the study team and consensus about the included items will be reached. The list will also be vetted with other communication experts in the field, with whom investigators of this project have established relationships.

Specific Aim 2: Develop the CommSense Software (Months 4-7)

Data Collection

The "ideal and optimal" list of communication metrics will be shared with engineering investigators to gauge technical feasibility. We anticipate this will be a highly iterative process between the engineering and clinical team investigators to refine our list of desired communication metrics based upon technical capabilities and clinical relevance. As discussed above (see Preliminary Work), CommSense will build upon prior work using an existing Android smartwatch platform (SWear) to collect sensor signals from smartwatches [57]. SWear collects multiple sensor streams such as motion, audio, and physiological data and synchronizes the data to a secure server for further analysis. SWear can also deliver microsurveys (Ecological Momentary Assessments) for collecting self-reported data. SWear has already been validated in multiple studies and is available on the Android play store [57,66]. CommSense will include sensing modules that can collect (1) physiological data via built-in sensors to measure variables such as heart rate, (2) gesture data via accelerometers and gyroscope sensors, and (3) voice data via the embedded microphone (see Figure 1). Although we recognize the importance of nonverbal communication and will thus leverage the existing passive sensing capabilities of CommSense to collect data related to heart rate variability and movement, these markers will be secondary to our primary focus of collecting audio data to analyze verbal and linguistic metrics of patient-provider communication.

Figure 1. CommSense system overview. Data are captured during patient-clinician interactions using smartwatches and synchronized to the secure cloud server to extract metrics characterizing communication quality, such as linguistic and paralinguistic markers (primary focus of the study) and physiological markers (secondary focus of study).



Specific Aim 3: Pilot Testing the Ability of CommSense to Accurately Extract Identified Communication Metrics (Months 8- 12)

Data Collection

CommSense will be piloted with 5 nursing or medical students and 5 experienced oncology/palliative clinicians (n=10) using simulated scenarios to evaluate its accuracy in capturing and extracting the preidentified communication metrics (Table 1). Each participant will work through 2 conversation scenarios (n=20,10 per group [84,85]) and we will collect multiple data points related to paralinguistic and linguistic markers, as well as body language and physiological markers (Figure 1). The primary goal of Aim 3 is to verify the fidelity of the data captured using CommSense by comparing findings to ground truth. Clinical team members will write 2 relevant scripted scenarios (approximately 10-15 minutes in length) that relate to assessing and managing cancer pain in a palliative care context. It is critical to emphasize that although we ultimately aim to advance communication evaluation beyond scripted and simulated scenarios, this pilot study represents the foundational first step to develop technology that can reliably capture and analyze communication data before being implemented "in the wild." Consistent with the scope of an exploratory pilot, this initial research will not involve real patients with protected health information. Future work with CommSense that involves actual patients will address all relevant privacy measures and the regulations of the Health Insurance Portability and Accountability Act of 1996. Pilot testing will occur in the institution's Clinical Simulation Labs. After consent and basic demographic data are obtained, participants will wear CommSense and enact the 2 scenarios. The "patient" for our pilot testing may be a voice-capable mannequin, a member of our study team, or an experienced clinician volunteer, depending on what is feasible considering COVID-19 restrictions. The interaction will be recorded by CommSense and by a separate fixed external microphone and recording device to establish ground truth. At the end of the interaction, participants will complete a brief survey to assess the acceptability of using CommSense, provide suggestions for future iterations, state preferences regarding data sharing, and rate their self-perceived communication performance.

Table 1. Examples of anticipated features to extract and analyze from conversations using CommSense.

Feature	Communication goal or rationale
Audio signal variables	
Silence	To allow time to process complex or difficult information
Speaking turns and interruptions	To avoid speech dominance and ensure all participants are heard
Prosody, flow, and rhythm	To reduce stress, and increase empathy and clarity
Natural language variables (primary)	
Complexity of language	To avoid medical jargon to decrease confusion
Tone or sentiment	To convey empathy, warmth, and openness, and build rapport
Open-ended versus close-ended questions	To allow exploration and promote bidirectional dialogue
Language associated with communication best practices related to palliative care and pain management (eg, "I want to be sure I understand…;" "It sounds like you are feeling…;" "Can you tell me more about…")	To use language associated with therapeutic communication related to symptom management in the context of serious illness
Nonverbal variables[a] (secondary)	
Heart rate, motion or movement, and gestures	To use nonverbal indicators (such as sitting down and not crossing arms) for establishing rapport, trust, and dialogue between the patient and provider, and heart rate for indicating provider stress level during conversation

[a]Due to the capability of the sensing platform and ease of collecting the data, nonverbal physiological and gesture-related variables will be collected, but they are not the primary focus of this study.

Data Analysis

CommSense data will be first preprocessed to clean the sensor data and extract markers of communication quality based on the metrics established in Aim 1. This will be achieved by analyzing (1) paralinguistic markers from the audio signals such as pitch, energy, and Mel-frequency cepstral coefficients to characterize features such as tone, silence, and speaking turns [86,87]; and (2) linguistic markers from the audio signals by first parsing the signal to text using Google's speech-to-text application programming interface. Then, several semantic features will be extracted using NLP methods such as word embedding features that can describe structural organization of words in the conversation (eg, frequency-based methods such as count vector and term frequency-inverse document frequency) and lexical features such as linguistic inquiry and word count, which is one of the most popular lexical feature extraction methods that has been rigorously validated in the context of psychometric analysis of textual data. We will also explore passively collected motion and physiological data, such as motion and heart rate data, and extract features that can characterize stress, such as heart rate variability. Finally, all the extracted linguistic, physiological, and motion-derived features will be analyzed to study how they fluctuate across scenarios

and groups using a multilevel analysis given the hierarchical structure of the data.

Establishing Ground Truth

Externally recorded conversations will be transcribed, verified, and then compared to the CommSense-generated output for the same conversation. To conduct this comparison, we will proceed in a stepwise manner. First, hard copy transcripts of the audio-recorded conversation will be independently coded using qualitative software by 2 clinical investigators to identify the communication metrics that we expect to be extracted by CommSense. Second, the results obtained by the 2 investigators will be compared to establish interrater reliability. If there is a discrepancy, a third team member will be consulted. Given concerns regarding the use of the Cohen κ [88] to evaluate interrater reliability, we chose verbal discussion to reconcile any potential disagreements between investigators regarding communication metrics identified in the transcripts. Third, we will compare the generated CommSense output with the ground truth investigator review of the same conversation. We will do this by assigning a numerical value based on the concordance between the CommSense output and the investigator review of the transcript. For each identified communication metric (eg, instances of overtalking) we will assign a score of 0 if the CommSense output does not match the investigator review of the hard copy transcript and a score of 1 if it does. For example, with 10 identified metrics, the best possible concordance score would be 10, meaning the CommSense output and the hard copy transcript review achieve 100% concordance. We will then calculate concordance scores for each conversation metric to achieve a composite score for each conversation to explore how accurately the CommSense software is able to extract the desired metrics from palliative care conversations. Descriptive statistics will be used to summarize demographic data and participant responses to the postdeployment survey assessing the acceptability of CommSense.

Ethics Approval

Institutional Review Board (University of Virginia Social & Behavioral Sciences IRB, #4985) approval has been granted.

Results

Work began on Specific Aim 1 in November 2021 and Specific Aim 2 in April 2022. Participant recruitment is expected to begin in summer 2022. We expect preliminary results to be available in fall 2022.

Discussion

Potential Applications of CommSense

We hypothesize that it will be feasible to extract relevant metrics of communication performance with >80% concordance between ground truth audio transcripts and the CommSense-generated output. We also hypothesize that health care providers will consider CommSense acceptable and helpful in improving their communication skills.

This pioneering idea represents a paradigm shift in health care delivery by leveraging a scalable and novel technology to measure, track, and evaluate patient-provider communication in the clinical setting. Consider the following potential scenario: A team of oncology health care providers from Clinic A complete intensive communication skills training and learn structured techniques to improve their ability to have difficult conversations with patients coping with advanced cancer. During the training, they practice these skills using scripted role plays. After the training, the health care providers in Clinic A are each given a CommSense wristband sensor (eg, smartwatch) to wear as they care for patients with advanced cancer in the actual clinic setting. With consent from all participants, the wristband sensor, equipped with multimodal sensors to capture natural language, is activated during patient-clinician conversations, and on-board processors capture, extract, and summarize preprogrammed metrics of interaction quality. Following the clinic visit, the wrist-worn device uploads summarized communication performance metrics for real-time display to the physician, nurse, and social worker. The physician is shocked to see that her speaking turns occupied 89% of the visit time and that she interrupted the patient 15 times. The nurse is pleased to see that her use of medical jargon has decreased to a single instance; however, she asked 3 times as many closed-ended questions compared to open-ended questions. The social worker realizes that yet again, he was the only health care provider who engaged the caregiver in discussing the pain management plan or addressed safe opioid handling practices at home. The entire team can collectively observe that their communication performance was not as strong as last week, but they are still performing at a higher level than 75% of their peer clinics. Additionally, as the individual and team communication performance in Clinic A improves, patients report lower pain scores. The trainers who led the communication skills training can track the progress of participants over time, assess the retention of communication skills over time, see how skills are being implemented "in the wild," and based on the results, they can better tailor future training sessions to meet the needs of participants. The hospital administrator is thrilled when she receives a monthly report that clearly shows oncology clinics using CommSense sensors have higher patient and caregiver satisfaction scores, fewer medication errors, and lower readmission rates.

The above scenario paints the long-range vision and potential impact of the CommSense technology. Although we propose to begin with 1 aspect of cancer care communication (pain management), we believe this model will be generalizable to other health care settings and contexts where quality communication is essential (eg, other types of high-stakes interactions, such as goals-of-care conversations or death notifications). We are eager to test CommSense in populations at high risk for health disparities and communication barriers (eg, patients from underrepresented groups experiencing undertreatment of pain), English as second language patients, and those at high risk for distressing symptoms (eg, patients with metastatic cancer). We also see key opportunities to customize this intervention for different metrics depending on the communication context, relevant outcome measures and communication preferences, and the needs and goals of participants. For example, different communication strategies may be needed for a patient who is an artist with pancreatic

cancer, does not speak English, and is being treated in a rural community hospital, compared to the communication strategies needed for a patient who is a physician, speaks English fluently, and is being treated at an academic medical center for routine gallbladder surgery.

Dissemination Plan

Results from this research will be presented at relevant technical and clinical academic conferences, as well as published in scholarly peer-reviewed journals. As we are a highly interdisciplinary team, our dissemination plan will aim to reach diverse audiences within nursing, medicine, and engineering domains. We also anticipate sharing findings with other key stakeholders (eg, clinicians, hospital administrators, and cancer advocacy groups) in more informal settings to continue developing the CommSense platform.

Limitations

The primary limitation of this study is that it is being conducted in simulated clinical scenarios rather than in real clinical settings. Although this is an important limitation to acknowledge, it is appropriate and essential to validate the functionality and feasibility of CommSense in simulated settings before implementing it in an actual patient care setting. Another important limitation is the inability of CommSense to completely capture the important and complex nuances (eg, subtle nonverbal cues) of patient-clinician communication.

Conclusions

This pilot study is poised to make a valuable contribution to communication science, and NLP and wearable computing capabilities. We see particularly exciting options to apply the CommSense technology to support effective virtual and remote patient-clinician interactions, which are likely to become more normative in our post-COVID world. Future steps include leveraging results to (1) implement CommSense in real clinical scenarios with a larger sample of participants to more robustly assess its feasibility and acceptability; (2) test CommSense with diverse high-risk, high-need populations and contexts and explore how to best customize the system using communication metrics tailored to patient, clinician, and organizational needs; (3) evaluate the impact of CommSense on relevant patient-centered and organizational outcomes, such as patient pain, medical errors, staff turnover, goal-concordant care and health care usage; (4) conduct experimental trials to test the effectiveness of CommSense in terms of pre- and postcommunication training versus standard of care; (5) determine how to best capture, integrate, and display nonverbal data relevant to communication such as position, eye contact, and gestures; (6) test multiple concurrent users of CommSense (eg, the clinician, patient, and family caregiver wearing CommSense during a conversation and receiving feedback) to evaluate the interactional aspects of communication; and (7) identify how to most effectively share collected data with key stakeholders (patients, caregivers, health care providers, and organizational units).

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by The Center for Engineering in Medicine, University of Virginia - Engineering-in-Medicine Seed Grant Program (Virginia, USA).
[PDF File (Adobe PDF File), 160 KB - resprot_v11i5e37975_app1.pdf]

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Abbreviations

NLP: natural language processing

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Protocol

Comprehensive Travel Health Education for Tour Guides: Protocol for an Exploratory Sequential Mixed Methods Research

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Abstract

Background: Tourists are at risk of experiencing health problems during their travel. However, even though tour guides have the potential to become travel health promoters, their participation has not been optimal.

Objective: This study aims to develop a comprehensive travel health education model to help tour guides improve health information delivery to tourists.

Methods: This is an exploratory sequential mixed methods research. The first phase consisted of a qualitative study with an informed grounded theory design. In-depth interviews were carried out with tour guides from all language divisions and policymakers of the Indonesian Tour Guide Association Bali Branch or Himpunan Pramuwisata Indonesia Daerah Bali (HPI Bali). The interview guidelines were developed based on the theory of planned behavior and identity theory. Qualitative data were analyzed thematically. In the interim phase, a travel health education model and questionnaire were developed based on the qualitative findings. The initial model and its instruments were finetuned after consultation with travel medicine and health promotion experts. Furthermore, the validity and reliability of the questionnaire were tested on 30 tour guides. The second phase consisted of a quantitative study with a randomized pretest-posttest control group design. A total of 76 tour guides in the intervention group received comprehensive travel health education, while 76 in the control group received no specific intervention. Outcome variables (ie, attitudes, subjective norms, perceived behavioral control, actual behavioral control, role identity, and behavioral intention) were measured at baseline (T_0), after the online training (T_1), before information sharing via WhatsApp (T_2), a month after the start of the WhatsApp intervention (T_3), and at the end of the WhatsApp intervention (T_4). The mean difference of each outcome variable before and after the intervention will be compared between the intervention and control groups. Thereafter, the quantitative and qualitative findings will be integrated into a joint display.

Results: The qualitative phase was conducted through in-depth interviews with 21 informants who included tour guides and policymakers from HPI Bali from May to June 2021. The education model, educational materials, and questionnaire were developed based on the qualitative findings and consultation with experts. The education model consists of online training and information sharing through WhatsApp and was trialed with tour guides from November 2021 to February 2022. As of April 2022, this study is in the quantitative data analysis stage.

Conclusions: A travel health education model was developed based on qualitative findings and consultation with experts. The model was tested with tour guides, and a series of self-administered questionnaires were completed. This study is in the quantitative data analysis stage and will continue by integrating qualitative and quantitative findings into a joint display.

Trial Registration: ClinicalTrials.gov NCT04961983; https://clinicaltrials.gov/ct2/show/NCT04961983

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KEYWORDS

travel health; health education; tour guides; tourists; health promotion

Introduction

Background

Tourists are an epidemiologically important population because they are potentially exposed to diseases outside their home country and may serve as a conduit for diseases from their origin to destination country or vice versa [1]. Tourists visiting tropical, subtropical, and developing countries, including Indonesia, are at a higher risk of morbidities and mortalities due to the lack of hygiene, sanitation, safety, and disease endemicity of the destinations [2-5].

Several studies in Australia revealed less than optimal pretravel health behavior of tourists visiting Southeast Asia, including Indonesia. There were low proportions of tourists seeking pretravel consultation, receiving malaria chemoprophylaxis, and receiving a vaccination for typhoid and hepatitis B [6-8]. According to the literature, health problems that tourists experience during their visits to Indonesia include diarrhea, tropical infections (eg, dengue hemorrhagic fever, typhoid, malaria), respiratory infections (including COVID-19), animal bites (ie, rabies), methanol intoxication, and injuries or trauma due to accidents in tourism sites or traffic accidents [3,9-17]. Mapping of safety hazards and risks based on the World Health Organization (WHO) criteria for 197 tourist attractions in Bali concludes that 6.6% are high-risk areas, 39.1% are moderate risk, and the rest are low risk [14,15].

These facts indicate that tourists need local, specific, and up-to-date information on the prevention of travel-related health problems to adopt appropriate prevention measures. A tour guide is one actor in the tourism industry that potentially delivers health information to tourists due to their intensive contact with tourists during their visits [18-20]. As one of the best-known tourism destinations in the world, Bali is a province with the highest number of international tourist visits in Indonesia [21]. Bali has a great potential to involve tour guides in travel health promotion because it boasts 5470 registered tour guides, which is more than half of the total number of tour guides in Indonesia [22]. However, a cross-sectional study in Bali suggested that about half of the tour guides in Bali never or rarely provide health information to the tourists they serve [23]. This indicates the need for improved tour guide behavior and a need to address its determinants, namely attitude, subjective norms, role identity, self-efficacy, and knowledge [23].

There is no published literature to date on interventions to improve tour guides' involvement in travel health promotion. Therefore, a comprehensive, relevant, and effective intervention addressing determinants of tour guides' behavior in providing travel health information should be developed. Accordingly, this study aims to develop a comprehensive travel health education intervention relevant to the needs of tour guides providing travel health information to tourists in Bali. In addition, this study aims to assess the efficacy of the intervention to improve tour guides' attitude, subjective norms, perceived behavioral control, actual behavior control, role identity, and intention to provide information regarding the prevention of travel health problems.

Theoretical Foundation

An integration of the theory of planned behavior (TPB) and identity theory was employed as the reference for developing the intervention because the constructs of these theories are relevant to the determinants of tour guides' behavior in travel health promotion [23-26]. TPB purports that human behavior is determined by three types of considerations: behavioral beliefs, normative beliefs, and control beliefs. Each of these beliefs will shape attitudes toward behavior, subjective norms, and perceived behavioral control, which in turn will affect behavioral intention. Behavioral intention and actual behavior control will ultimately determine the implementation of a particular behavior [26,27].

TPB has been used extensively in the development of behavior change interventions in the last three decades, including in the health sector [28-30]. TPB is used in this study because the delivery of travel health information by tour guides is a planned and voluntary behavior influenced by both internal and external determinants. There are limited publications related to the application of TPB in interventions to change actors' individual behavior to become health promoters with the primary purpose of changing the health behavior of others [29,30]. The application of TPB to interventions that target nonhealth actors to make them health promoters in the context of travel health is even less explored, calling for further study [31].

A tour guide's role as a nonhealth actor is a determinant that can influence their health-promoting behavior. Therefore, this research proposes an extended TPB by integrating identity theory into TPB [28]. The travel health education model developed in this study is a comprehensive intervention as it targets all determinants of health behavior based on the construct of extended TPB.

Methods

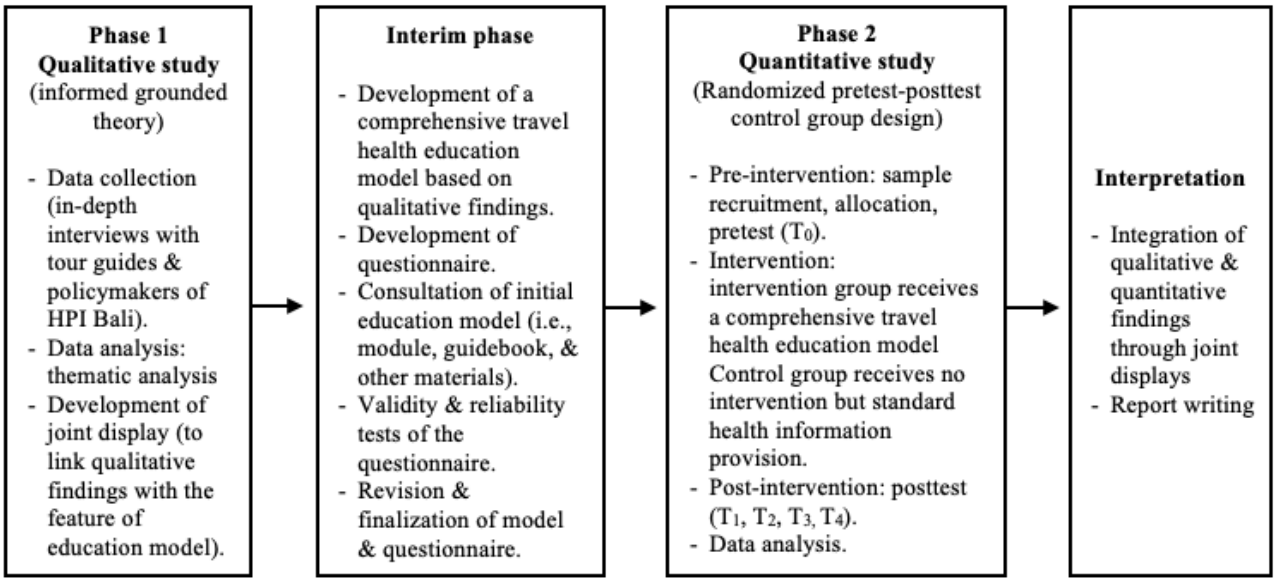
Trial Registration

This study was registered in ClinicalTrials.gov (NCT04961983).

Study Design

This research employs an exploratory sequential mixed methods design, in which the collection and analysis of qualitative data are conducted prior to the quantitative data [32,33]. The qualitative study results in the first phase became the basis for the intervention development in the interim phase. The intervention was then tested for its efficacy in the quantitative study. The workflow is presented in Figure 1.

Figure 1. Workflow of an exploratory sequential mixed methods study to develop a travel health education model.



Study Setting and Population

This study was conducted in Bali, Indonesia. The study population comprised of 5470 tour guides who are registered members of the Indonesian Tour Guide Association Bali Branch or Himpunan Pramuwisata Indonesia Daerah Bali (HPI Bali).

Phase 1: Qualitative Study

Study Design

The first phase of this research consisted of a qualitative study with an informed grounded theory, a design in which processes and products are developed in accordance with grounded theory but informed by existing theoretical frameworks [34].

Informants

At the beginning of this study, purposive sampling was employed, a nonrandom method ensuring that particular categories of informants within the population were represented in the study [35]. Informants were recruited based on the category of language division. There are 11 language divisions in HPI Bali: English, Japanese, Korean, Mandarin, France, Dutch, Italian, Spanish, Russian, German, and Indonesian. Every language division in HPI Bali has its own market countries (eg, tour guides in the English language division serve tourists from English-speaking countries). Therefore, 11 tour guides from all language divisions of HPI Bali were interviewed to gain a comprehensive understanding of the health education needs of tour guides serving tourists from various countries. In addition to the tour guides, we conducted in-depth interviews with 2 policymakers from HPI Bali to explore more perspectives regarding a feasible and relevant travel health education model to address tour guides' needs. Based on the ongoing data analysis results, 8 tour guide informants were recruited using theoretical sampling, recruitment based on data that require further exploration [35]. These informants were recruited through HPI Bali or snowballed from the previously interviewed informants. The prospective informants received an explanation of the research, and those who were willing to participate were asked to provide written consent.

Interview Guides

Questions for the semistructured interview guide were developed with reference to the constructs of the TPB, which was integrated with the identity theory. The interviews explored the following themes:

- Health problems experienced by tourists during their visit
- Attitude, subjective norms, perceived behavior control, role identity, actual behavioral control, and intention to provide information regarding travel health
- Provision of travel health information to tourists and barriers faced in conveying the information
- Tour guides' needs for travel health information
- Educational strategies pertinent to tour guides' needs (content, mode of delivery, duration, setting, supporting facilities)

All topics were explored through open questions. The order of questions was flexible according to each informant's response during interviews. Other information outside the interview guide that was interesting and important was also explored by the interviewers.

Data Collection

Data collection was carried out in person following COVID-19 health measures (ie, wearing masks and physical distancing) in the place and time agreed by the informant and interviewer. Interviews were audio recorded with the informants' consent. Data collection and analysis were conducted concurrently. Recruitment of informants were stopped when the data reach theoretical saturation, the point at which no new theoretical insight emerges [35].

Data Analysis

The qualitative data were analyzed using inductive thematic analysis, in which the researcher identifies patterned themes [36]. Thematic analysis steps include interview transcription, familiarization of data, open coding of the entire data, axial coding (identifying the association of codes and integrating associated codes into a thematic category), selective coding

(selecting and integrating categories into main themes to construct a theory), and report writing. The report also contained a joint display to link the qualitative findings with the detailed components of intervention design. Strategies to increase the trustworthiness of the research findings included triangulation of sources and peer debriefing with experts in travel health and health promotion [33]. NVivo 12 Plus software was utilized in the data analysis process.

Interim Phase

In the interim phase, the qualitative findings were used to develop an intervention in the form of a travel health education model and its instruments (ie, travel health promotion guidebook for tour guides, training module, and media for WhatsApp information sharing), as well as a questionnaire to be tested in the quantitative study. The integrative procedure in this study was represented in a joint display. Joint display explicitly presents how the codes and themes that emerged in qualitative research have shaped the intervention elements [32]. The initial education model, its instruments, and the questionnaire were refined after consultation with travel medicine, health promotion, and tour guiding experts who provided input regarding the content and delivery formats. The questionnaire then underwent a pilot test on 30 tour guides. The validity and reliability of the questionnaire were analyzed, and revisions were made accordingly.

Phase 2: Quantitative Study

Study Design

The research then continued with a quantitative strand using an experimental randomized pretest-posttest control group design. The intervention group received intervention in the form of a comprehensive travel health education model, while the control group received no intervention but standard health information provision.

Participants

The minimum sample size in this study was calculated by employing the WHO Sample Size Determination software using the formula of a 1-tailed hypothesis test for a difference in two population means [37]. Using the parameters d=10.0, μ1=71.2, μ2=66.2, α=.05, and 1–β= 90% and taking into account a dropout rate of 10%, the minimum number of samples for each intervention and control group was 76. Sample selection was carried out with disproportionate stratified random sampling from the list of tour guides who were HPI Bali members. The selected tour guides were contacted to determine if they met the eligibility criteria. Those who did were given a further explanation of the research and asked to sign the informed consent form if they were willing to participate.

Eligibility Criteria

Samples for the quantitative research were recruited according to the following inclusion criteria: registered members of HPI Bali, age 55 years old or younger, working as a tour guide for 1 year or more, own a smartphone and/or computer with Zoom and WhatsApp applications, and familiar with Zoom and WhatsApp usage.

The exclusion criteria included the following: holding structural positions in HPI, having a formal health education background, unwilling to work as a tour guide after the reopening of tourism, and reluctant to participate in the study. In addition, the dropout criteria included those who did not fully participate in the intervention and could not be contacted due to illness or other reasons at the time of data collection.

Assignment of Intervention

A study statistician employed permuted block randomization technique to assign the participants to the intervention and control groups [38]. The research group assignment was communicated to the research team member, who informed and managed the participants' enrollment and intervention assignment. A strategy to improve participants' adherence to the intervention protocol was to elucidate the benefits of full participation in this study, including the provision of a completion certificate, credit for the internet, and compensation for the time allocated for participating in the online training. In addition, adherence monitoring was performed by inspecting the participants' attendance and participation in each education session.

Study Outcomes

The outcomes of this study referred to the constructs of integrated TPB and identity theory, including attitude, subjective norms, perceived behavioral control, actual behavioral control, behavioral intention, and role identity. A summary of the outcomes is presented in Table 1.

In addition to those outcome variables, several variables were controlled by analysis, namely age, sex, education, length of work, employment status, tourists' country of origin, and type of tourism activities.

Table 1. Summary of study outcomes.

Study outcomes	Definition	Data measurement and analysis scale	Data source (time point)
Attitude	Psychological tendencies expressed by the tour guides regarding providing travel health information to tourists	• Measurement scale: ordinal (Likert scale) • Data analysis scale: interval	Self-administered questionnaire (T_0, T_1, T_2, T_3, T_4)
Subjective norms	Tour guides' perception of the extent to which providing travel health information to tourists is something that is expected by the tourists they serve, their employers (travel agents), HPI[a], and the community	• Measurement scale: ordinal (Likert scale) • Data analysis scale: interval	Self-administered questionnaire (T_0, T_1, T_2, T_3, T_4)
Perceived behavioral control	Tour guides' confidence in their ability to provide travel health information to tourists	• Measurement scale: ordinal (Likert scale) • Data analysis scale: interval	Self-administered questionnaire (T_0, T_1, T_2, T_3, T_4)
Actual behavioral control	Tour guides' knowledge regarding the prevention and first aid of travel health problems	• Measurement scale: ordinal (Likert scale) • Data analysis scale: interval	Self-administered questionnaire (T_0, T_1, T_2, T_3, T_4)
Role identity	Tour guides' perception of the extent to which travel health promotion is a part of their role	• Measurement scale: ordinal (Likert scale) • Data analysis scale: interval	Self-administered questionnaire (T_0, T_1, T_2, T_3, T_4)
Behavioral intention	Tour guides' willingness to provide travel health information to the tourists they serve	• Measurement scale: ordinal (Likert scale) • Data analysis scale: interval	Self-administered questionnaire (T_0, T_1, T_2, T_3, T_4)

[a]HPI: Himpunan Pramuwisata Indonesia (Indonesian Tour Guide Association).

Data Collection

Quantitative data collection was carried out through self-administered questionnaires. The outcome variables were measured at 5 time points: at baseline (T_0), immediately after the online training (T_1), a month after training and before information sharing via WhatsApp (T_2), a month after the start of WhatsApp information sharing (T_3), and two months after WhatsApp intervention or at the end of intervention (T_4). All participants in the intervention and control groups were asked to simultaneously fill out digital questionnaires (Google Forms) at a particular time determined by the researcher. Instructions for filling out the questionnaire were listed at the beginning of each questionnaire section to prevent incorrect or incomplete responses. Reminders via SMS and WhatsApp were sent to participants to ensure that the questionnaire was filled. There was no specific data monitoring committee established in this study due to the limited study scale and available resources. Data monitoring was undertaken by an appointed member of the research team (author NMSN).

Questionnaires

The instrument used to collect the quantitative data was a self-administered questionnaire. The same questionnaire was utilized for both the pretest and posttest and consisted of 7 sections: sociodemographic and job characteristics, attitude, subjective norms, perceived behavioral control, actual behavioral control, role identity, and behavioral intention.

The statements in the questionnaire to measure outcome variables were developed based on an integration of TPB and identity theory as well as the results of the qualitative strand. Alternative responses for each statement were presented on a 7-point Likert scale ranging from strongly disagree to strongly agree. Meanwhile, the actual behavioral control was measured using questions related to knowledge regarding prevention and first aid of travel-related health problems, with “right,” “wrong,” and “do not know” options.

Data Management and Analysis

Quantitative data were extracted from the digital questionnaires and transferred to the database. Coding was done to the extracted data, and data values were checked by two data analysts. Data without participants' names were exported into a file format suitable for analysis with statistical software. The electronic data were stored on a computer protected with a password and only accessible to the research team.

Quantitative data will be analyzed descriptively by calculating the frequency distribution for categorical data as well as the total scores, mean, median, standard deviation, and range of minimum to maximum scores on numerical data. The comparability of the intervention group and the control group in terms of control variables will be analyzed using the chi-square test for categorical data and independent *t* test or Mann-Whitney *U* test for numerical data [39-41]. Data normality will be calculated using Kolmogorov-Smirnov test. Additionally, data homogeneity will be tested using the Levene test [39,42]. A complete case analysis will be performed to handle missing outcome data.

The mean comparison test will be conducted to determine mean differences between the intervention and the comparison groups.

Repeated measures analysis of covariance (ANCOVA) will be employed because the measurement of dependent variables was conducted repeatedly at 5 time points, and there are covariates that need to be controlled in the analysis [39].

Data Integration

Mixed methods research employs various approaches and data collection and analysis methods, which are integrated to answer a research question. Therefore, integration between the qualitative and quantitative approaches during the research process is a defining feature of mixed methods research [43]. The integration procedure in this study will be carried out through the development of joint displays that will demonstrate the relationship between quantitative and qualitative findings [32,43]. The joint display procedure aims to interpret how the results of quantitative research support the quality and the appropriateness of the context and culture of an intervention developed specifically for a particular population [32].

Ethics Approval

This study received ethical clearance from the Institutional Review Board of the Faculty of Medicine, Udayana University/Sanglah General Hospital (number 1419/UN14.2.2.VII.14/LT/2021). The informed consent procedure was followed, and written consent was provided by the participants. Data obtained throughout the research process were kept confidential and stored in computers and cabinets only accessible to the research team. The participants' anonymity was upheld by not including their names or other identifiable characters in transcriptions, research reports, or publications.

Results

Qualitative data collection was conducted from May to June 2021. There were 21 informants including tour guides from 11 language divisions and the head and secretary of HPI Bali. Qualitative findings revealed some negative behavioral, normative, and control beliefs that influenced tour guides' lack of intention and behavior. Moreover, their role as "nonhealth actors" informed their low intention to provide health information to tourists. A lack of knowledge regarding prevention and first aid of frequent travel-related health problems was also documented.

A comprehensive travel health education model was developed at the interim phase (July to October 2021). The instruments of the model, namely the training module, guidebook, and media for WhatsApp information sharing, were designed based on the qualitative findings. These instruments were further finetuned after consultation with travel medicine and health promotion experts. The questionnaire was also tested for its validity and reliability with 30 tour guides. Refinements to the questionnaire were made according to the results.

The travel health education model includes 10 hours (2 days) of online training via Zoom and weekly travel health information sharing via the WhatsApp group for 2 months. The training content and format were included in the training module (Figure 2). The topics covered in the training included:

- The importance of travel health information for tourists
- The potential role of tour guides in tourists' health
- Assessment of tourists' health risks
- Prevention and first aid of general travel-related health problems, water and foodborne diseases, allergic reactions, respiratory tract infections (including COVID-19), mosquito and other insect bites, rabid animal bites, snake bites, stings and punctures from marine animals, methanol poisoning, sexually transmitted infections, and trauma or injury
- Health and safety hazards of tourist attractions and travel health facilities in Bali
- Communication techniques in travel health promotion to tourists

The training materials were delivered by travel medicine, health promotion, and medical emergency experts. Participants also received a travel health guidebook containing information on the prevention and first aid of various travel-related health problems (Figure 2).

WhatsApp information sharing was initiated in December 2021, a month after training. Participants were invited to a WhatsApp group and received weekly travel-related health information for 2 months. Participants asked questions and shared their experiences in the WhatsApp group. A moderator answered the questions and facilitated discussions among the participants. A total of 76 tour guides in the intervention group fully participated from the beginning to the end of the intervention (November 2021 to February 2022). An identical number of tour guides in the control group received no intervention but completed a series of self-administered questionnaires.

Figure 2. Training module and travel health guidebook.

Discussion

Initial Findings

This study aims to develop a comprehensive, relevant, and effective travel health education model for tour guides. The model is comprehensive because it addresses all determinants of behavior according to TPB and identity theory. This model is also relevant to tour guides' needs because it was developed with active participation from tour guides and accommodated their perceptions and preferences. The results of 21 in-depth interviews were used to develop the components of the initial travel health education model. The qualitative results of this mixed methods study confirm the findings of a cross-sectional study on tour guides in Bali showing that improvements should be made in tour guides' provision of travel health information to tourists [23]. The qualitative data also indicate a need to address the determinants of travel health information provision to tourists, namely tour guides' attitude, subjective norms, perceived behavioral control, role identity, actual behavioral control, and intention. The education content was developed using information on tour guides' normative beliefs, behavioral beliefs, control beliefs, role identity, and information regarding various health hazards and health problems encountered by tourists throughout their travel.

Tour guides in Bali have limited exposure to information on the prevention and first aid of travel-related health problems. Most of the informants showed a preference for training as a direct and interactive way of obtaining information regarding travel health. Due to the COVID-19 pandemic and its resultant public health measures, online training is more feasible and safer to implement than traditional face-to-face learning. Moreover, online training can be provided to tour guides residing outside Bali. Many tour guides moved back to their hometown during the pandemic because Bali is currently closed for international tourism. Training was complemented with information sharing via WhatsApp to maintain the retention of acquired information and enable further discussion. WhatsApp is considered an appropriate platform for education because it is the main communication platform used in HPI Bali.

Participation in the quantitative study was challenged by the fact that many tour guides have become jobless and are facing economic challenges due to COVID-19. Therefore, the participants were given internet credit and compensated for their time. All participants in the intervention and control groups fully participated in this study. No conclusions regarding the effectiveness of this model could be made because this study is still in the quantitative data analysis phase.

Comparison to Prior Work

Published literature on interventions to improve the involvement of tourism actors in travel health promotion is still limited. Most of publications so far have been observational studies focusing on the travel health-related knowledge, attitude, and practices of actors in the tourism sector [23,44-47]. There was an experimental study in Canada examining the effectiveness of a health promotion model in the form of providing brochures, pamphlets, and website to improve travel agents' referral behavior to travel clinics for pretravel consultation [31]. However, a comparison could not be made with this study due to the different target population, targeted behavior changes, and setting.

Strengths and Limitations

The strength of this study lies in its use of an exploratory sequential mixed methods design. The qualitative strand enables a broad and in-depth exploration of the perspectives and experiences of tour guides and is expected to produce a

comprehensive and relevant model. Meanwhile, the quantitative strand provides evidence of the model's efficacy. The mixed methods design of this study can justify the efficacy, context, and cultural appropriateness of the education model developed specifically for tour guides [32].

This study has novelty as the first mixed methods research that aims to develop a travel health education model for tour guides and was developed by systematically referencing TPB integrated with identity theory [24,25]. Therefore, it is also expected to provide a theoretical advantage for the development of TPB.

This study also has some limitations. First, the education model was developed based on the experiences and perspectives of tour guides in Bali. Therefore, the content covered in this education model might not reflect the needs of all the tour guides in Indonesia because it is an archipelago with varied health situations. However, tour guides in Bali comprise more than half of tour guides in Indonesia. Tour guides in Bali, especially those proficient in languages rarely mastered by tour guides in other provinces (ie, Spanish, French, Russian, Korean, and Dutch), also provide overland tour guiding services to other parts of Indonesia. Therefore, their perceptions may also accommodate the travel health education needs of tour guides in other tourist destinations in Indonesia.

The second study limitation is that all study outcomes were measured through a self-administered questionnaire, which is a subjective measurement tool. Thus, there is a probability of participants providing normative answers that could have influenced data validity. Moreover, because this research was carried out amid the COVID-19 pandemic when tourist visits were still very limited, measurement of behavior could not be carried out.

Future Directions

As of April 2022, this study is in the quantitative data analysis phase. The quantitative results will be integrated with the qualitative findings in a joint display to conclude on the efficacy of the intervention that was specifically designed according to the needs and context of tour guides in Bali. This study is expected to expand the amount of scientific evidence to optimize the involvement of actors in the tourism industry in travel health promotion. Therefore, at the end of this study, its findings will be disseminated through research reports, publications in journals, conferences, and public forums at national and international levels.

This study will resume once tourism in Bali has recovered and measure the effect of this intervention on tour guides' provision of health information. An investigation into the effect of tour guides' health information to tourists, as the primary target of the intervention, will also be conducted. Some of the targeted outcomes to measure the efficacy of the intervention are tourists' knowledge, attitude, practice, and incidence of health problems. Tourists' perceptions and acceptance of tour guides delivering travel health advice is another aspect that warrants further investigation and will be used to develop more appropriate and effective strategies.

Conclusions

This exploratory sequential mixed methods study aims to develop a comprehensive, relevant, and effective travel health education model for tour guides to improve their travel health promotion behavior. A travel health education model comprising online training and information sharing via WhatsApp was developed based on the qualitative findings and in consultation with experts. The intervention was trialed with tour guides, and a series of self-administrated questionnaires was completed. After the completion of quantitative data analysis, the qualitative and quantitative findings will be integrated into a joint display to conclude on the efficacy of the education model.

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Authors' Contributions

NMSN conceptualized the study protocol, and PPJ and IMAW refined the study protocol. NMSN wrote the initial draft of the manuscript, and PPJ, IMAW, and IMB edited the manuscript. All authors reviewed, edited, and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the Doctoral Program of Medical Sciences, Faculty of Medicine, Udayana University (Jalan Panglima Besar Sudirman, Denpasar, Bali, Indonesia).
[PDF File (Adobe PDF File), 414 KB - resprot_v11i5e33840_app1.pdf]

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Abbreviations

ANCOVA: analysis of covariance
HPI: Himpunan Pramuwisata Indonesia
TPB: theory of planned behavior
WHO: World Health Organization

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Protocol

Using Artificial Intelligence to Revolutionise the Patient Care Pathway in Hip and Knee Arthroplasty (ARCHERY): Protocol for the Development of a Clinical Prediction Model

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Abstract

Background: Hip and knee osteoarthritis is substantially prevalent worldwide, with large numbers of older adults undergoing joint replacement (arthroplasty) every year. A backlog of elective surgery due to the COVID-19 pandemic, and an aging population, has led to substantial issues with access to timely arthroplasty surgery. A potential method to improve the efficiency of arthroplasty services is by increasing the percentage of patients who are listed for surgery from primary care referrals. The use of artificial intelligence (AI) techniques, specifically machine learning, provides a potential unexplored solution to correctly and rapidly select suitable patients for arthroplasty surgery.

Objective: This study has 2 objectives: (1) develop a cohort of patients with referrals by general practitioners regarding assessment of suitability for hip or knee replacement from National Health Service (NHS) Grampian data via the Grampian Data Safe Haven and (2) determine the demographic, clinical, and imaging characteristics that influence the selection of patients to undergo hip or knee arthroplasty, and develop a tested and validated patient-specific predictive model to guide arthroplasty referral pathways.

Methods: The AI to Revolutionise the Patient Care Pathway in Hip and Knee Arthroplasty (ARCHERY) project will be delivered through 2 linked work packages conducted within the Grampian Data Safe Haven and Safe Haven Artificial Intelligence Platform. The data set will include a cohort of individuals aged ≥16 years with referrals for the consideration of elective primary hip or knee replacement from January 2015 to January 2022. Linked pseudo-anonymized NHS Grampian health care data will be acquired including patient demographics, medication records, laboratory data, theatre records, text from clinical letters, and radiological images and reports. Following the creation of the data set, machine learning techniques will be used to develop pattern classification and probabilistic prediction models based on radiological images. Supplemental demographic and clinical data will be used to improve the predictive capabilities of the models. The sample size is predicted to be approximately 2000 patients—a sufficient size for satisfactory assessment of the primary outcome. Cross-validation will be used for development, testing, and internal validation. Evaluation will be performed through standard techniques, such as the C statistic (area under curve) metric, calibration characteristics (Brier score), and a confusion matrix.

Results: The study was funded by the Chief Scientist Office Scotland as part of a Clinical Research Fellowship that runs from August 2021 to August 2024. Approval from the North Node Privacy Advisory Committee was confirmed on October 13, 2021. Data collection started in May 2022, with the results expected to be published in the first quarter of 2024. ISRCTN registration has been completed.

Conclusions: This project provides a first step toward delivering an automated solution for arthroplasty selection using routinely collected health care data. Following appropriate external validation and clinical testing, this project could substantially improve the proportion of referred patients that are selected to undergo surgery, with a subsequent reduction in waiting time for arthroplasty appointments.

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KEYWORDS

orthopedics; prediction modelling; machine learning; artificial intelligence; imaging; hip; knee; arthroplasty; health care; patient care; arthritis

Introduction

Background

Hip and knee osteoarthritis (OA) is a common and disabling condition that predominantly affects the older population. Within Scotland, the prevalence of OA among people aged >45 years is approximately 10% and 17% for hip and knee OA, respectively [1]. The associated pain and loss of function can be so severe that over 10% of patients report their health state as being "worse than death" [2]. Joint replacement or "arthroplasty" provides a very successful method of improving symptoms for those with end-stage OA [3]. However, there are substantial current waiting times for surgery across the United Kingdom, and it is often difficult for nonspecialists such as general practitioners (GPs) to determine who might benefit from operative intervention.

Programs such as Active Clinical Referral Triage have attempted to address this problem through senior clinical decision-making instead of triage. However, this is labor and time intensive, with hospital consultants challenged by the difficulty of accessing and integrating the wealth of available, routinely collected health care data. Artificial intelligence (AI) provides a new, exciting, and hitherto unexplored technology to address these problems, with the potential to rapidly, and correctly, prioritize patients for arthroplasty. The ability to include automated analysis of radiological images into predictive models is particularly unique and may be of great benefit in this clinical context. The automated stratification of patients based on routine electronic health data could streamline referrals and reduce waiting lists through improved system efficiency.

The potential of AI techniques to address the current challenges of arthroplasty service provision is particularly important given that the number of people with end-stage OA continues to rise alongside an aging population [4]. In 2019, over 15,000 hip and knee arthroplasty operations were performed in Scotland alone [5], with an anticipated increase of over 100% for both primary total knee arthroplasty and total hip arthroplasty in the United Kingdom from 2005 to 2030 [6]. As a result, the numbers of revision total knee arthroplasty and total hip arthroplasty are expected to rise by over 300% [6], placing even greater demand on arthroplasty services.

Current service demand levels are already placing a substantial strain on the National Health Service (NHS). Many trusts throughout the United Kingdom set arbitrary thresholds for patient-reported outcome measures (PROMs) or BMI to limit arthroplasty referrals, despite evidence that current thresholds are likely inappropriate and exclude patients who would benefit from surgery [7,8]. Furthermore, over 61% of patients still currently wait between 3-9 months for clinical review prior to surgery (unpublished Scottish national survey data), with significant increases expected in the future due to service disruption and the backlog associated with the COVID-19 pandemic [9].

In addition, there are major difficulties for nonspecialists in determining who may benefit from operative intervention, as the majority of patients lie in the middle of the clinical need curve. As a consequence, less than 50% of new patients seen in an arthroplasty clinic are deemed suitable for surgery (unpublished Scottish national survey data). The resulting prolonged waiting times for review and subsequent surgery then have a negative impact on patient health [10] and potentially create greater strain on primary care and physiotherapy services. These negative changes that occur during the preoperative period also significantly impact the potential health gains imparted following hip and knee arthroplasty surgery, with greater deterioration seen for those with longer wait times [11]. The subsequent lower levels of physical activity may have long-term, wide-ranging implications for general health and well-being [12], with a significant associated economic and societal impact [13].

These adverse consequences stem from an inability to correctly and rapidly select suitable patients for surgery; therefore, a new method of streamlining arthroplasty referrals to reduce wait times is urgently needed. In this paper, we will build upon the work done within Scotland through the Active Clinical Referral Triage toward providing a personalized and precise arthroplasty service. The use of AI and machine learning techniques within orthopedics is an expanding field and provides an excellent method of analyzing integrated data from multiple clinical information sources, such as those required to improve arthroplasty care pathways. By transforming the way that arthroplasty services are delivered, timely access to appropriate and cost-effective care could be achieved, thus reducing complications and improving long-term physical function with a substantial impact on key stakeholders.

Primary Objectives

1. Develop a cohort of patients with referrals by GPs regarding assessment of suitability for hip or knee replacement, and collect laboratory, clinical, and imaging data from NHS Grampian via the Grampian Data Safe Haven (DaSH).
2. Determine the demographic, clinical, and imaging characteristics that influence the selection of patients to undergo hip or knee arthroplasty, and develop a tested and validated patient-specific predictive model to guide arthroplasty referral pathways.

Methods

The AI to Revolutionise the Patient Care Pathway in Hip and Knee Arthroplasty (ARCHERY) project will be conducted through 2 linked work packages designed to deliver on the project objectives.

Work Package 1: The Definition of a Grampian Regional Data Source and the Establishment and Validation of a Linked Orthopedic Health Care Data Set Using Routinely Collected Data

The first work package will use ready to access local regional data from NHS Grampian that combines routine administrative data systems with enriched local data. Similar linked data sets have been used extensively by the team at the Aberdeen Centre for Health Data Science, within which the candidate will be hosted. Techniques for data access and processing are described in detail later in the protocol. Patient demographic information (Standard Morbidity Record 01 [SMR01]), medication records (prescribing information system), laboratory data (Apex hematology and biochemistry), COVID-19 data, theatre records (Centricity Opera) and PROMs (local PROMs database) will be used to develop the core algorithms using combinations of the relevant clinical codes (eg, International Classification of Disease 10th Revision [ICD-10] or Office of Population Censuses and Surveys Classification of Interventions and Procedures version 4 [OPCS-4]). SMR01 and theatre records (Centricity Opera) will provide the main resource for identifying joint replacement through the relevant ICD-10 codes. Unstructured (eg, free text) information in clinical letters and radiology image data will be used to validate and enhance these detailed characterizations. Risk factors and outcome measure algorithms will also be developed and validated against electronic clinical records.

Clinical knowledge of the key parameters involved in surgeon decision-making regarding patient selection for arthroplasty operations, as well as a planned systematic review, will aid variable selection. Given the standardization of referrals through the national Scottish Care Information Gateway system and the widespread similarities in approach to joint replacement selection throughout the United Kingdom, the use of Grampian regional data should produce a model that is widely applicable. Furthermore, we will use the close links between the Industrial Centre for Artificial Intelligence Research in Digital Diagnostics (iCAIRD) sites in Aberdeen and Glasgow to ensure that all data sources used have relevance regarding potential future suitability for national application.

Subsequent operation and automation of these techniques will allow for systematic and reproducible approaches to characterize the key clinical features of the data that are relevant to orthopedics. The algorithms created will then be scaled and used to appropriately categorize and construct a linked data set, covering all relevant hospital episode data on patients with orthopedic referrals, that will be used in work package 2.

Work Package 2: The Development of a Clinical Prediction Model to Help Guide Arthroplasty Selection

Using the cohort developed in work package 1, probabilistic and classification machine learning will be conducted through statistical analysis software programs (Rstudio [Rstudio PBC], Python, and Tensorflow [Google]) to predict whether or not a patient would be selected to undergo surgery based on preoperative clinical data (including imaging data and reports, clinical letters [through natural language processing], patient health care information, and PROMs). This will also include information about the patients' likelihood of having a successful outcome, both in terms of functional improvement and avoidance of complications.

The machine learning models will use data from the predictive variables that were isolated from the preoperative routine health care data and described in work package 1. Pretrained convolutional neural networks (a type of machine learning categorized as deep learning) will be used for X-ray images to significantly increase generalizability, with the X-ray images providing the foundation for model creation. To facilitate model training, development, and internal validation, we will use k-fold cross-validation, allowing all data to be used for testing and internal validation purposes without sample attrition.

Model Output

The machine learning model will create 2 types of output for the primary outcome–a classification model, where the output is a discrete binary selection, and a probabilistic model. This will provide different possibilities for future clinical application depending on key stakeholder input; the algorithm could either be used as an adjunct in the patient-GP clinical discussion and decision-making process regarding referral or as a postreferral triage system, where patients are stratified to see different orthopedic specialists based on their predicted suitability for surgery.

Data Access and Processing

The project will be performed within the remit of the Grampian DaSH. This is located within the Aberdeen Centre for Health Data Science, which has considerable expertise and experience working across local, regional, and national systems for projects. Study outcomes of the proposed work will be shared through social media engagement, dissemination at relevant conferences, and publication.

Safe processing of NHS patient data using AI will be provided through collaboration with iCAIRD—a pan-Scotland collaboration of 15 partners, including the Universities of Aberdeen and Glasgow, and a world-class center of excellence for AI application to health care within Scotland. The project will use the iCAIRD Safe Haven Artificial Intelligence Platform located within the NHS domain to perform the machine learning analysis.

Although individual patient data cannot be shared, the metadata and information about the data access procedure and the data extraction methods will all be shared through online repositories (eg, GitHub).

Recruitment

There will be no direct participant recruitment for this study. Unconsented, pseudo-anonymized data will be used. Inclusion criteria are defined as individuals aged ≥16 years who have been referred for the consideration of elective primary hip or knee replacement within NHS Grampian from January 2015 to January 2022. This cohort will be generated from Scottish Care Information–stored referral letters by identifying the patients who have been referred to elective orthopedic services within NHS Grampian and have the words *"hip" OR "knee" AND "arthritis" OR "pain"* (including stemming: eg, "osteoarthritis") as free text information contained within the referral letter. This process will occur prior to data access by the study team. Exclusion criteria are defined as the following: individuals who have undergone revision hip or knee arthroplasty, arthroplasty at another site, or unicompartmental knee replacement; individuals who have undergone hip or knee replacement for trauma (hip fracture or distal femoral fracture); and individuals who have undergone operative management outside of NHS Grampian.

The research team will have no access to patient identifiers, such as name, date of birth, or Community Health Index. No identifiers will leave the NHS server. Identifiable data will be stored in DaSH on an NHS server with access restricted to NHS Health Intelligence analysts and approved DaSH analysts (with NHS Grampian honorary contracts).

Deidentified data (ie, data without patient identifiers) will be stored on a dedicated DaSH secure server with access to the data restricted to the named, approved DaSH staff who will prepare the data.

Access to the anonymized data will be via virtual private network, as per DaSH processes, and within a secure analytics platform using restricted access to high power computer clusters. The computers used will have limited access measures in place via usernames and passwords.

The project has a DaSH data management plan, which provides details of how the data will be transferred, managed, stored, and accessed (Multimedia Appendix 1).

Data linkage and management will be completed in DaSH using accredited procedures to collect, link, and pseudo-anonymize the electronic data and enable users to securely access the anonymized data and back up and recover data. The data linkage plan for the project is displayed in Multimedia Appendix 2.

The legal basis for processing unconsented personal data is covered by the condition set out in Article 6 (1) (e) of General Data Protection Regulation (GDPR) [14]: "[the condition for] processing [personal data is that it] is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller" (ie, processing is necessary for the University's public interest task of conducting research).

The basis for the processing of sensitive personal data is outlined in Article 9 (2) (j) of GDPR [14]: "processing is necessary for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes."

Sample Size

Sample size will be set by the number of patients that have sufficient data available; this is anticipated to be approximately 2000 patients from an initial screening of the records. It has previously been noted that over 90% accuracy can be achieved with a minimum of 500 samples when considering the development of convolutional neural networks, and accuracy increases with the size of the training cohort [15].

Using the guidance for binary clinical prediction models provided by Riley et al [16], we anticipate that this sample size will:

1. Estimate the overall outcome proportion with sufficient precision, which required a sample size of 384 with an outcome proportion of 0.5 and a margin of error of 0.05.
2. Target a small mean absolute prediction error, which required a sample size of 1890 with 20 candidate predictors, an outcome proportion of 0.5, and a mean absolute prediction error of 0.050.
3. Target a shrinkage factor of 0.9, which required a sample size of 800 with an R^2 value of 0.2 [17], 20 candidate predictors, and a target S value of ≥0.9.
4. Target a small optimism of 0.05 in the apparent R^2 value, which required a sample size of 36 with an anticipated R^2 value of 0.2, an outcome proportion of 0.5, a maximum R^2 value of 0.75, and 20 candidate predictors.

Analysis

First, descriptive analyses of the generated cohort will be performed to evaluate the base characteristics, including the assessment of any missing data. The type and size of missing data will determine whether any formal data imputation techniques are required. If necessary, this will be done using multiple imputations by chained equations. Data fields with large volumes of missing data will be assessed using complete case analysis.

Univariable analyses will be performed to assess the association between the final included variables and outcomes. *t* tests and Mann-Whitney *U* tests will be used for parametric and nonparametric continuous data, respectively, and chi-square tests will be used for categorical data. In all tests, $P<.05$ will denote significance. The results will be reported with 95% CI.

Initial model development will consist of the use of raw imaging data alone, followed by sequential inclusion of variables deemed to be important from the univariable analyses and background clinical knowledge identified from key literature searching.

Multiple models will be generated, with evaluation performed through standard techniques such as the C statistic (area under curve) metric, calibration characteristics (Brier score), and a confusion matrix. The model that performs best against these domains will be chosen. A κ index will be used to compare the ability of the machine learning algorithms to detect severe arthritis requiring joint replacement against human observers using an observer-defined clinical categorization tool (Kellgren-Lawrence grading). Heat maps will be generated as part of the machine learning output to identify the areas of the

included images that have contributed primarily to model classification using a technique called class activation mapping.

All analyses will be performed using R statistical software (R Foundation for Statistical Computing) as a base program, with additional input from other programs, such as Tensorflow and Python, as required.

Ethics Approval and Conduct

Informed consent has not been sought, which is consistent with other studies performing retrospective review of pseudo-anonymized health data. The chief investigator and staff involved with this study will comply with the requirements of the GDPR [14] and Data Protection Act 2018 [18] with regards to the collection, storage, processing, and disclosure of personal information and will uphold the Act's core principles.

The data will be managed by DaSH, the accredited regional safe haven for NHS Grampian, and in accordance with existing Caldicott and Research Ethics Committee approvals for DaSH. Linkage and anonymization will follow standard, approved, and accredited protocols and will be undertaken by DaSH staff.

The research team will undertake appropriate information governance training before gaining access to a dedicated DaSH research analytics platform.

Approval from the North Node Privacy Advisory Committee was confirmed on October 13, 2021 (Multimedia Appendix 3). This covers approvals from the following organizations: NHS Grampian Caldicott Guardian, Research Ethics Committee, NHS Grampian Research & Development, NHS Grampian Information Governance, and University of Aberdeen Research Governance.

All data, reports, and other records will be used in a manner designed to maintain participant confidentiality. The study will be conducted in accordance with the 1964 Helsinki declaration and its later amendments.

The chief investigator and staff involved with this study will not disclose or use the study data for any purpose, other than for the work described in this protocol and related documentation.

Results

The study was funded by the Chief Scientist Office Scotland as part of a Clinical Research Fellowship that runs from August 2021 to August 2024.

Data collection started in March 2022, with the results expected to be published in the first quarter of 2024. ISRCTN registration has been completed (number 18398037).

The conduct and reporting of the study will be in-line with the Transparent Reporting of a Multivariable Prediction Model of Individual Prognosis or Diagnosis–Artificial Intelligence (TRIPOD-AI) statement, which is currently in the final stages of development [19].

Discussion

Expected Findings

We anticipate the development of an automated internally validated algorithm from routine health data that will provide a first step toward improving the selection of patients for referral to undergo hip and knee arthroplasty surgery.

This new pathway will help to maximize efficiency through improved quality of care and reduced administrative burden for clinical staff. This is particularly important in the context of the COVID-19 pandemic that has already seen substantial increased pressure placed on arthroplasty services.

Comparisons to Prior Work

Other clinical research within this area is very limited. Many trusts throughout the United Kingdom set arbitrary thresholds for PROMs or BMI to limit arthroplasty referrals, despite evidence that current thresholds are likely inappropriate and exclude patients that would benefit from surgery.

Strengths and Limitations

The strengths of this study include the availability of substantial volumes of relevant clinical data through the creation of a regional linked data set. The use of machine learning analysis and, particularly, the inclusion of clinical imaging data within a predictive model are novel and provide potential for improvement over pre-existing techniques. The development of automated systems using routine health data will ensure minimal additional burden and maximize cost-efficiency.

Limitations include the use of retrospective data collection, which limits the scope and type of information collected, as well as the need for further evaluation and development before use in clinical practice can be considered.

Future Directions

Once developed, the prediction model will have to undergo external validation to ensure it retains its potential utility outside of NHS Grampian data. This will likely take place using the federated iCAIRD network, which would allow the deployment of the developed model algorithms to use NHS Greater Glasgow and Clyde data without the need for any data transfer out of the local safe haven environment.

The externally validated model will then be required to undergo assessment regarding the potential impact on clinical practice, ideally through a randomized controlled trial design. Input from key stakeholders, such as those in primary care, will be integral to ensuring that any model maximizes the potential for clinical impact through application at the correct stage of the patient journey.

Once in clinical practice, continual evaluation and further development of the model will be required to ensure that a high level of clinical applicability across populations is maintained.

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Diane Smith (patient partner) in the development of the study protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Data management plan.
[DOCX File , 35 KB - resprot_v11i5e37092_app1.docx]

Multimedia Appendix 2
Data linkage plan.
[DOCX File , 118 KB - resprot_v11i5e37092_app2.docx]

Multimedia Appendix 3
North Node Privacy Advisory Committee Approval.
[PDF File (Adobe PDF File), 179 KB - resprot_v11i5e37092_app3.pdf]

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Abbreviations

AI: artificial intelligence
ARCHERY: AI to Revolutionise the Patient Care Pathway in Hip and Knee Arthroplasty
DaSH: Data Safe Haven
GDPR: General Data Protection Regulation
GP: general practitioner
iCAIRD: Industrial Centre for Artificial Intelligence Research in Digital Diagnostics
ICD-10: International Classification of Disease 10th Revision
NHS: National Health Service
OA: osteoarthritis
OPCS-4: Office of Population Censuses and Surveys Classification of Interventions and Procedures version 4
PROM: patient-reported outcome measure
SMR01: Standard Morbidity Record 01
TRIPOD-AI: Transparent Reporting of a Multivariable Prediction Model of Individual Prognosis or Diagnosis–Artificial Intelligence

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Protocol

The Association Between Sleep Disturbance and Suicidality in Psychiatric Inpatients Transitioning to the Community: Protocol for an Ecological Momentary Assessment Study

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Abstract

Background: Patients are at high risk of suicidal behavior and death by suicide immediately following discharge from inpatient psychiatric hospitals. Furthermore, there is a high prevalence of sleep problems in inpatient settings, which is associated with worse outcomes following hospitalization. However, it is unknown whether poor sleep is associated with suicidality following initial hospital discharge.

Objective: Our study objective is to describe a protocol for an ecological momentary assessment (EMA) study that aims to examine the relationship between sleep and suicidality in discharged patients.

Methods: Our study will use an EMA design based on a wearable device to examine the sleep-suicide relationship during the transition from acute inpatient care to the community. Prospectively discharged inpatients 18 to 35 years old with mental disorders (N=50) will be assessed for eligibility and recruited across 2 sites. Data on suicidal ideation, behavior, and imagery; nonsuicidal self-harm and imagery; defeat, entrapment, and hopelessness; affect; and sleep will be collected on the Pro-Diary V wrist-worn electronic watch for up to 14 days. Objective sleep and daytime activity will be measured using the inbuilt MotionWare software. Questionnaires will be administered face-to-face at baseline and follow up, and data will also be collected on the acceptability and feasibility of using the Pro-Diary V watch to monitor the transition following discharge. The study has been, and will continue to be, coproduced with young people with experience of being in an inpatient setting and suicidality.

Results: South Birmingham Research Ethics Committee (21/WM/0128) approved the study on June 28, 2021. We expect to see a relationship between poor sleep and postdischarge suicidality. Results will be available in 2022.

Conclusions: This protocol describes the first coproduced EMA study to examine the relationship between sleep and suicidality and to apply the integrated motivational volitional model in young patients transitioning from a psychiatric hospital to the community. We expect our findings will inform coproduction in suicidology research and clarify the role of digital monitoring of suicidality and sleep before and after initial hospital discharge.

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KEYWORDS

sleep; suicide; psychiatric inpatient; ecological momentary assessment; EMA; experience sampling; coproduction; sleep disturbance; discharge

Introduction

Suicidal Ideation and Behavior After Psychiatric Hospital Discharge

The prevention of suicide is a well-established goal for patient safety and a national and global public health priority. Suicide risk is increased after discharge from a psychiatric hospital [1], regardless of previous suicidal behavior. In the United Kingdom, there were 1988 deaths by suicide between 2008 and 2018 within 3 months of discharge from inpatient care, which amounts to 15% of all suicides [2]. Suicide is most frequent in the first week following discharge, making the transition period from hospital to the community one of the riskiest for suicidal behavior in adults and young people. In fact, this risk is highest on day 2, yet follow up with support services sometimes does not occur until day 7 [3]. Thus, the first week is a critical period for immediate aftercare and treatment planning following discharge from psychiatric inpatient care. The risk is significantly increased in patients with various individual factors, including previous self-inflicted violence (eg, self-harm and suicidal behavior), intoxication, and health conditions. Risk is further elevated when patients experience insomnia, nightmares, or sleep disturbance that results in being awake at night [4]. This is particularly troublesome as immediate support (eg, clinical services or social support networks) is typically limited during the night.

The Relationship Between Sleep, Suicidal Ideation, and Behavior

There is increasing evidence that sleep dysfunction is an independent risk factor for suicidal ideation and behavior (SIB) [5]. Several systematic reviews have explored the epidemiological relationship between sleep and SIB in different population groups (eg, in mixed samples [6], nonpsychiatric adolescent patients [7,8], and psychiatric patients [9]), examined prospective suicide incidents, and more recently, explored the underlying mechanisms of this relationship [9]. All these studies have showed a strong correlation between sleep and SIB; however, most studies have been cross-sectional or retrospective in design. The temporal nature of the relationship between sleep disturbance and suicidality was the focus of the most recent systematic review [10]. Of the 41 included studies, only 1 measured insomnia as a predictor of suicidal ideation in real time (over a 24-hour period) in the United Kingdom [11]. The lack of studies may be due to the challenge and expense of monitoring sleep and suicidality without using self-reported data. However, the scarcity of data is problematic, since both sleep and suicidality fluctuate; therefore, current studies do not account for temporality [12-15].

Measuring Sleep and SIB in Real Time Using Technology

Ecological momentary assessment (EMA) is an intensive self-report method that can be used to assess experiences, symptoms and behaviors in real-time at multiple times of the day [16,17]. EMA monitors people within their natural environment, usually with the aid of a smartphone or wearable smart device (such as a wrist-worn electronic watch) to reduce recall bias, leading to greater efficiency, ecological validity, and accuracy than more traditional research methods [18]. The use of EMA in the study of SIB has shown great promise because of its ability to monitor and identify proximal factors (eg, sleep) associated with SIB in daily routines; the use of EMA has increased dramatically in the last 5 years [19,20]. However, only a few EMA studies have been conducted in high-risk groups with experience of suicidal ideation and behavior during inpatient hospitalization or following discharge [12,21-24]. Most recently, Glenn and colleagues [22,25] performed an EMA study with a 28-day period to examine the relationship between sleep and suicidality in adolescents (12-18 years old) following discharge from acute psychiatric care in the United States. Notably, EMA was deemed feasible in this high-risk group, with adherence being highest in the first week following discharge; participants found that wearing an actigraphy device (eg, a wearable device to measure the sleep-wake cycle) was acceptable. Similarly, EMA has also been deemed feasible to measure SIB in patients undergoing community mental health support [25] and acceptable as a data collection method in young adult cohorts [25,26]. However, to our knowledge, no studies have used EMA to monitor sleep and suicidality during the transition from psychiatric inpatient care to the community.

Application of Sleep to the Integrated Motivational Volitional Model

While there is increasing evidence of a prospective relationship between sleep problems and suicide, not everyone who experiences sleep problems will develop suicidal thoughts and behavior, or vice versa. Therefore, it is vital to investigate the underlying mechanisms by which disturbed sleep may lead to suicidality. The integrated motivational volitional (IMV) model is an established theoretical model that proposes that people transition from ideation to suicidal behavior because of the complex interplay of multiple factors, including core psychological mechanisms, such as defeat and entrapment, and background factors (eg, life events such as being in hospital) [27,28]. Littlewood and colleagues [29] recognised the potential importance of suicidal imagery (ie, “flashforwards” of future events involving one’s suicide or the aftermath of death) when studying the relationship between sleep and suicide. Moreover, suicidal imagery might also trigger entrapment or hopelessness, resulting in suicidal ideation and behavior [28,29]. These

conceptualizations are promising, but to date have not been examined in young adults transitioning from the hospital to the community. This proposal therefore presents a unique opportunity to address these gaps in research and patient safety in this vulnerable population.

The primary aim of this paper is to describe and outline an exploratory EMA study protocol that examines sleep as a possible measure of deterioration and a potential predictive factor for SIB in young patients during the transition period from an inpatient setting to the community. We will address the following research questions: (1) Is there a difference between predischarge and postdischarge sleep in young adult patients? (2) Does sleep disturbance pre- and postdischarge predict postdischarge SIB in young patients? and (3) Is it acceptable and feasible to use EMA to monitor SIB postdischarge in young adults?

We hypothesize that there will be a difference between pre- and postdischarge sleep in young patients (this is hypothesis 1). Additionally, based on previous research, we hypothesize that sleep disturbance (ie, insomnia and short sleep duration) postdischarge will predict SIB while controlling for depression and baseline sleep (this is hypothesis 2). We will also explore the conceptual model in our patient sample; we expect that sleep disturbance will be associated with defeat, entrapment, and hopelessness postdischarge (this is hypothesis 3). We also expect that EMA will be deemed both feasible and acceptable for inpatients transitioning from the inpatient setting to the community.

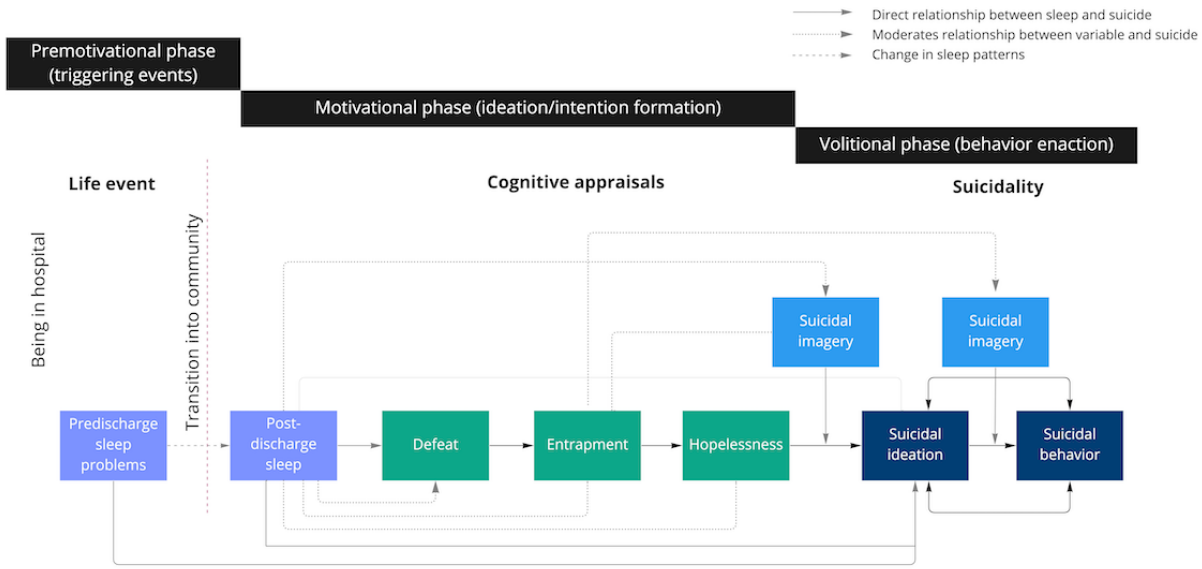
Methods

Study Design and Setting

This is a prospective, repeated-measures EMA study with inbuilt evaluation. Wrist-worn digital devices will be used to explore the relationship between sleep and SIB during an acute psychiatric transition while also evaluating defeat, entrapment, hopelessness, and suicidal imagery. Our conceptual model integrates key aspects of the IMV model [27,28] and is one of only two psychological models to integrate sleep [29] (Figure 1).

Recruitment will take place in 2 acute psychiatric hospitals in West London that provide support and care for mental health problems or mental health crises (Hammersmith and Fulham Mental Health Unit and Lakeside Mental Health Unit). EMA using smartphones is a practical option; however, it is difficult to accurately measure the sleep-wake cycle with this method [30] and there are potential privacy issues [31] in retrieving data due to connectivity; moreover, some patients might not have access to a smartphone within an acute hospital environment in England. Hence, we opted for the Pro-Diary V device (Camntech), which has inbuilt actimetry, and short questionnaires as the most viable options for accuracy and ease of use within the flow of daily life.

Figure 1. Adapted conceptual model of sleep and suicide in young transitioning inpatients.



Ethics Approval

This study received ethical approval from South Birmingham Research Ethics Committee (21/WM/0128) on June 28, 2021. The study will be registered on the Observational Studies Register.

Eligibility

Participants will be inpatients in an acute psychiatric ward due to be discharged within a 4-week period, age 18 to 35 years old, with a diagnosis of a mental disorder confirmed by the Structured Clinical Interview from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, in their clinical records [18]. Participants will be excluded if they are outside the age range, not fluent in English, or using sleep medication (ie, hypnotic medication such as zopiclone or zolpidem). We will not exclude participants on anxiolytics (ie, benzodiazepines) as most patients discharged will likely be on medication with some sedative effect.

Recruitment

Clinicians at West London National Health Service (NHS) Trust (WLT) will initially approach eligible participants in the acute psychiatric hospitals participating in the study. Prospective participants will be given an information sheet and asked if they would be happy for a researcher to approach them. If they agree, a trained researcher will approach them, explain the study, and answer any questions. After at least 24 hours, the patient will be approached for a second time to ask if they would be happy to take part in the study; consent will then be obtained.

Procedure

Following screening and informed consent, key demographic factors will be collected via medical records. These will include gender, age, ethnicity, marital status, length of time in hospital, mental health diagnosis, prescribed medication (historic and current), sleep history, family history of suicide, previous suicidal thoughts, and suicide plans and attempts. The researcher will then administer the baseline questionnaires face-to-face at a date and time convenient to the participant.

The researchers will then brief each participant during a 15-minute one-on-one session on the purpose of the Pro-Diary V watch, procedures needed to complete the study, and the method of using the watch, and will give accompanying written guidance on how to use the wearable device (eg, not to take the watch off unless having a shower or bath, how to use the menus, and how to answer the questions). The researchers will show the participants a demonstration version of the Pro-Diary V watch (demo beeps will be enabled for user training), and will prompt the participants with a timed questionnaire to allow the participants to learn the operation of the device. The participants will not need to charge the watch, as it has a battery life longer than the duration of the data collection period. The researchers will go through the written guidance with the participants to make sure they have a good understanding of what is expected of them and will answer any questions they might have. Selected onsite staff at each inpatient unit will be trained in the use of the watch and will assist the participants daily until discharge.

The participants will wear the watch for a maximum of 14 days, including 1 to 4 days before discharge, to determine the baseline profile and a minimum of 10 days after discharge (ie, the riskiest period for SIB and death by suicide). During this period, the watch will prompt each participant 4 times per day by vibrating to answer brief questions (Figure 2, Figure 3). The start point of the daily prompts will be decided by each participant based on their sleep-wake schedule. The start point of the day will normally be 30 minutes after their usual waking time. Between-prompt intervals will be delivered using a fixed time sampling schedule. Fixed time points were chosen to reduce study burden in this high-risk group of participants and increase compliance. Participants will be able to delay the prompt for 20 minutes if they are not able to answer straight away (eg, if they are undergoing inpatient activity). Each participant will receive a £15 (US $18.78) e-voucher after each stage (ie, they will receive a voucher after baseline assessment, after EMA, and after follow-up assessment), following a suggestion by our young coresearchers.

Figure 2. Study schedule. EMA: ecological momentary assessment.

	Inpatient						Community										
	Days																
	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Enrollment																	
Information	*																
Eligibility screen	*																
Informed consent		*															
Instructions on Pro-Diary V use		*															
Given Pro-Diary V		*															
Assessments																	
Baseline		*															
EMA (days 1-14)			*	*	*	*	*	*	*	*	*	*	*	*	*	*	
Follow-up																	*
Adverse events		*							*							*	
Follow-up																	*
Check ins and debrief																	
Researcher check in						*					*					*	
Debrief																	*

Figure 3. Example of Pro-Diary V watch with question about suicidal ideation.

After discharge, the participants will receive 2 follow-up calls (once a week) to resolve any problems arising from the EMA method and the use of the watch, including technical issues, and to answer any queries from the participants, following existing guidance [32]. The researchers will contact the participants again toward the end of the EMA period to arrange a date to administer the follow-up questionnaires. The researchers will administer the questionnaires face-to-face in a private room at a WLT community site at a time convenient to the participant. At the end of the study period, deidentified EMA data will be collected from each participant, downloaded to a secure enclave at Imperial College London, and analyzed within the secure platform.

Patient and Public Involvement

This study will build on our extensive experience of working with young people with mental health difficulties [26,33,34] to conduct meaningful patient and public involvement. We issued a call for young people with experience of psychiatric inpatient care and suicidality (eg, ideation or behavior) in November 2020 through existing advisory groups, email distribution lists, and social media (eg, Twitter) and asked prospective participants to fill out a short application form. After internal selection, 3 participants were selected to inform most research stages, serving as coresearchers. These coresearchers were consulted on (1) design and ethics, (2) recruitment, (3) management, (4) data interpretation, (5) dissemination of findings, and (6) evaluation. The coresearchers have already reviewed the research documentation (eg, the information sheet, protocol, and consent form) and subsequently, changes were made to the documents. For example, the language was revised into plain English and the "nightmares" variable was added to the design. A recruitment poster was also coproduced with the coresearchers. One coresearcher also attended the NHS Research Ethics Committee meeting. The coresearchers have been trained in a basic understanding of EMA and sleep. Based on a suggestion from a previous coresearcher, [26] we expect to cofacilitate a face-to-face "meet and greet" event at the acute hospital for the research team to meet the potential study participants and encourage participation. We have set up a project-specific WhatsApp (Facebook Inc) group to make sure everyone is easily involved in decision-making, and we will have 4 virtual team meetings per year on Zoom (Zoom Inc). Coresearchers will also be listed as coauthors on all study outputs, including academic papers. Disclosure and Barring Service certificates have been obtained or are currently being obtained for coresearchers to ensure that all are deemed capable of safely interacting with patients with mental health difficulties.

Baseline and Follow-up Questionnaires

Participants will complete a baseline assessment (Table 1) that will cover sleep with the Sleep Condition Indicator (SCI) and Pittsburgh Sleep Quality Index (PSQI) [35,36], nightmares with the Disturbing Dream and Nightmare Severity Index [37], sleep environment with the Hospital Environment Sleep Questionnaire [38], affect with the Positive and Negative Affect Scale [39], depression with the Patient Health Questionnaire (PHQ-9) [40], anxiety with Generalized Anxiety Disorder-7 scale [41], defeat and entrapment with the Short Defeat and Entrapment Scale [42]), mental imagery with the Impact of Future Events Scale [43], and lifetime suicidal and nonsuicidal ideation and behavior with the Self-injurious Thoughts and Behavior Interview [44]. Additional follow-up questions will cover medication use, access to hospital and primary care, and informal or formal support received since discharge. Questions on the acceptability of using EMA and a wearable device to monitor the transition were adapted from another study that used EMA (questions included, for example, "I found the questions easy to understand" [45]) or were included after discussion with the study authors and our wider team. Feasibility will be measured by participation rate, adherence to the EMA protocol, and adherence to wearing the device.

Table 1. Baseline and follow-up measures.

Variable	Questionnaire	Items	Scoring	Used at baseline, follow up, or both
Sleep environment	Hospital Environment Sleep Questionnaire	16	0-64	Baseline
Sleep	Sleep Condition Indicator	8	0-32	Both
Sleep	Pittsburgh Sleep Quality Index	19	0-21	Both
Nightmares	Disturbing Dream and Nightmare Severity Index	6	Unique to item	Both
Affect	Positive and Negative Affect Scale	20	10-50	Both
Depression	Patient Health Questionnaire-9	9	0-27	Both
Anxiety	Generalized Anxiety Disorder-7 scale	7	0-21	Both
Mental imagery	Impact of Future Events Scale	24	0-96	Both
Defeat and entrapment	Short Defeat and Entrapment Scale	8	0-16 for defeat and 0-16 for entrapment	Both
Lifetime and current suicidal and nonsuicidal self-injury ideation and behavior	Self-injurious Thoughts and Behavior Interview-Short Form	N/A[a]	Unique to item, including open ended, counts, and 0-4 scale	Baseline (lifetime) and follow up (current only)
Feasibility and acceptability	Bespoke questionnaire designed to measure feasibility and acceptability of ecological momentary assessment for mental health following discharge	10	1-50 and open ended	Follow up

[a]N/A: not applicable.

EMA Measures

EMA items were selected according to use in previous studies [46], adapted from standardized measures, or taken from the experience sampling methodology (ESM) item repository [47] (Table 2 and Table 3). Some were adapted after discussion with the young coresearchers. For example, “Right now, I am feeling suicidal” was revised to “Right now, I feel suicidal,” as it was deemed simpler to read and more in line with the structure of the other items. Similarly, questionnaire density, sampling scheme, and momentary assessment frequency were informed by the considerations of the coresearchers, by the characteristics of the high-risk population, and by previous literature. Previous literature shows that participants in studies with a shorter duration and a lower number of question prompts per day had higher compliance [48]. Therefore, we considered that minimizing the number of prompts per day and limiting the study period to 14 days would result in the highest participant compliance rate [21]. We discussed this idea with the coresearchers and decided that 4 was a reasonable number of prompts. This was based on consideration of the high-risk population and an opinion that 4 prompts did not impose an undue burden and would still provide enough data to capture different times of the day.

Table 2. Ecological momentary assessment measures. Measures were taken 4 times daily and used a 7-point Likert scale, ranging from 1 ("not at all") to 7 ("very much so").

Variable	Item
Suicidal ideation [11]	• Right now, I feel suicidal
Self-harm ideation [46]	• Right now, I feel like harming myself without the intention to die
Defeat [42]	• Right now, I feel defeated by life • Right now, I feel powerless
Entrapment [42]	• Right now, I feel trapped • Right now, I want to escape my emotional pain
Positive affect[a]	• Right now, I feel excited • Right now, I feel cheerful • Right now, I feel satisfied • Right now, I feel relaxed
Negative affect[a]	• Right now, I feel stressed • Right now, I feel irritated • Right now, I feel anxious • Right now, I feel sad • Right now, I feel insecure • Right now, I feel hopeless

[a]Taken from the experience sampling methodology (ESM) item repository [47].

Table 3. Daily measures.

Variable	Item	Frequency	Response scale
Suicidal behavior	I tried to kill myself today	Last beep of the day	Binary[a]
Self-harm	I have self-harmed today	Last beep of the day	Binary
Suicidal imagery	I have had images of making a suicide attempt today	Last beep of the day	Binary
Self-harm imagery	I have had images of hurting myself today	Last beep of the day	Binary
Nightmares [49]	Did you have nightmares of a traumatic experience last night?	First beep of the day	Binary
Subjective sleep parameters [50]	What time did you get into bed?	First beep of the day	Time
	What time did you try and to go to sleep?	First beep of the day	Time
	How long did it take you to fall asleep?	First beep of the day	Minutes
	How many times did you wake up, not counting your final awakening? In total, how long did these awakenings last?	First beep of the day	Number
	What time was your final awakening?	First beep of the day	Time
	What time did you get out of bed for the day?	First beep of the day	Time
	How would you rate the quality of your sleep?	First beep of the day	Likert[b]

[a]In binary scales, 0 indicated "no" and 1 indicated "yes."

[b]Five-point Likert scale, ranging from 1 ("very poor") to 5 ("very good").

Objective and Subjective Sleep Parameters

A total of 5 key parameters will be objectively measured via inbuilt actimetry in the Pro-Diary V watch: total sleep time, sleep efficiency, wake after onset, sleep latency, and the number of awakenings. The same parameters will be measured through self-reporting using the Pro-Diary V software sleep diary, based on the Consensus Sleep Diary [50], to validate the objective reporting. This is recommended practice to establish the key period for analyzing sleep parameters [51].

Statistical Analysis

The lme4 and nlme R CRAN packages (CRAN R Project) for mixed effects models will be used. We will measure subjective sleep and objective sleep (via actigraphy) separately; this will be accounted for in independent models. Suicidal ideation will be measured multiple times a day. We will calculate the next-day worst point levels (eg, the highest score each day) for the suicide parameters [22] (eg, postdischarge sleep and early morning suicidal ideation), as this is deemed to be the best predictor of suicidal behavior [52]. In the first instance, analysis will be

conducted to answer the primary research questions and hypotheses with specified confounders. A secondary analysis will be conducted for more exploratory work and to determine the conceptual model relationships between subjects and data. To address hypothesis 1, we will analyze both person-level baseline sleep problems (determined by the SCI and PSQI) and within-person sleep diary predictors (determined by EMA and actigraphy). We will first compare baseline sleep problems for mean values and follow-up mean values with the *t* test. Next, we will conduct a linear regression analysis to examine the grand-mean centered daily level (within-person) sleep diary variables from the night before (total sleep time, sleep efficiency, wake after onset, sleep quality, sleep latency, the number of awakenings, and nightmares) in the inpatient hospital (days 1-4) and post-discharge sleep parameters by data number (ie, time-related variables). A similar approach will be taken with the actigraphy data. To address hypothesis 2, all models will have random intercepts and use either postdischarge worst-point suicidal ideation across any day (days 5-14) or day-level suicidal behavior. Our first mixed effects model will include EMA (day level) sleep parameter predictors: total sleep time, sleep efficiency, wake after onset, sleep quality, sleep latency, the number of awakenings, and "nightmares." Our second mixed effects model will add person-level variables, including baseline sleep (SCI and PSQI) and depression (PHQ-9). Our final model will add in the interactions between ESM day-level parameters and person-level variables that are significant ($P<.05$). The same models will be applied for the secondary outcomes (nonsuicidal self-injury ideation and behavior), and objective sleep parameters (the actigraphy data). We will then explore the conceptual model and specifically address hypothesis 3. We will use separate mixed effects models to examine the impact of EMA (momentary) entrapment, defeat, and hopelessness on awakening suicidal ideation (the start of day prompt) while moderating for each day-level sleep parameter predictor (EMA and actigraphy).

Sample Size Calculation

Sample size calculations for EMA studies differ from traditional calculations due to the inherent multi-level structure of the design, with multiple assessment periods. However, to answer our primary research question (ie, "Does sleep disturbance pre- and postdischarge predict postdischarge SIB in young patients?), we need to calculate our sample size based on 3 levels of data: momentary assessments nested within days, nested within persons. Specifically, these are day-level observations of suicide (the worst point level for suicidal ideation among 4 momentary assessments) and sleep. In the absence of pilot data for this specific population, we estimated sample size based on several factors. First, the only 2 (to our knowledge) ESM studies [11,22] that examined sleep and suicide with similar clinical populations had roughly 50 participants (N=48 and N=51, respectively). Second, from this, we noted that a sample size of 50 was recognized as an acceptable sample size number for multi-level analyses, in line with guidance and simulation studies [53]. Third, we entered a sample size of 50 into an EMA calculator [54] to estimate the power with 14 days and 1 response (the worst point level of suicidal ideation) per day. This showed that a total of 50 participants was sufficient to achieve 90% power and detect large effect sizes, allowing for a 75% completion rate. To guard against possible dropout or incomplete EMA completion, we will dedicate time to the initial EMA briefing session with the participants and regularly check in with them to help maximize retention, in line with previous guidance [55] Notably, to our knowledge, few ESM studies have given justifications for sample size; therefore, we have tried to be as transparent as possible about our calculations. We will also extend the recruitment period if required. If there are missing data, we will apply maximum likelihood estimation to allow all data to be testable across the multilevel modeling.

Ethical Approval, Considerations and Safeguarding

Ethical approval was obtained from NHS Ethics Committee and Health Research Authority (21/WM/0128). Upon discharge, as part of standard care, participants will receive a leaflet containing key contact details for their community support team and an additional booklet containing key numbers for each relevant informal support service (eg, Shout and Samaritans). These were co-designed with young people with lived experience. Participants will also be contacted by a member of the community mental health team within a week of discharge.

All participants involved in the study will be assessed for suicidal ideation and behavior at each EMA assessment using brief questions. After each assessment, a message will be displayed on the Pro-Diary V watch giving them contact information for their mental health services. This will be either their clinical team or the 24-hour single point of access (telephone number 0300 1234 244 in the United Kingdom); they will also be advised to go to the emergency department at their nearest hospital or call Shout—a 24-hour, 7-day-a-week crisis text line (available at 85258 in the United Kingdom) that aims to bring texters from a "hot moment" to "cool calm" through active listening and collaborative problem solving. Live, trained crisis counsellors receive text messages and immediately respond from a secure online platform. Participants will also be called by the researcher every week for a study check in.

Throughout the study, participants may be become incapacitated or rehospitalized and will therefore will be unable to continue. If this happens, we will contact the participant, if we are able to, and collect the wearable device. If we cannot contact the participant, we will ask the study inpatient clinician to collect it for us. We will explain that the data collected up until the point of being rehospitalized will be included in the data analysis, in line with the consent form and information sheet declaration.

Results

Study recruitment was due to start in November 2021, and we expect results to be available in 2022. To date, we have reflected on the working relationship with the young coresearchers across each research stage. Researcher and coresearcher reflections indicate that establishing and maintaining a safe environment for open discussion and continued communication (eg, via a WhatsApp group) have been vital to effectively share power and decision-making. Safeguarding and support needs for both

coresearchers (eg, an individualized strategy) and researchers (eg, clinical supervision) have also been particularly evident. To date, the coproduced design, recruitment poster, documentation (eg, the information sheet, protocol, and consent form), and this research paper have demonstrated significant impact.

Discussion

EMA is a promising methodology that could monitor and identify factors (eg, sleep) associated with suicidality. In our qualitative study, we found that wearables were deemed acceptable and feasible by young patients to monitor sleep and activity and to detect mental deterioration [26]. However, it is unknown if wearables can be used in the real world to measure sleep and activity. This study is a unique opportunity to address these gaps in research and patient safety in this vulnerable population. We expect to find a relationship between poor sleep and next-day suicidal ideation. If successful, we expect to build on this work and examine this relationship, determining mechanisms with the adapted IMV model in a larger study sample. We also expect to implement and test sleep treatment for transitioning high-risk young patients to reduce suicidality.

There are potential key limitations to our study. First, our study sample is small. While adequately powered for our within-sample analyses, it will be less powered for the between-subjects analyses. Second, most momentary analyses will be exploratory, and we therefore will not be able to give a precise impression of the application of the adapted IMV model to sleep. However, we expect to develop this work in the future and conduct more highly powered studies. Lastly, unlike the gold standard measure of polysomnography, actigraphy cannot characterize a full sleep architecture. However, it does provide an objective measurement of sleep that is obtained within a natural environment, increasing ecological validity.

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Authors' Contributions

LD led on conceptualization, patient and public involvement, project management, and drafting and finalizing the paper. MS and SP provided clinical guidance on project setup and safeguarding. TG and TW advised on statistical analysis. TG advised on ecological momentary assessment methodology and analysis. LD, JC, LM, MH, MDS, SP, PA, TG and TW co-designed the study and reviewed and approved the final paper.

Conflicts of Interest

PA is the principal investigator for a research grant provided by Dr Foster Ltd (a wholly owned subsidiary of Telstra Health). No other authors declare any competing interests.

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Abbreviations

EMA: ecological momentary assessment
ESM: Experience Sampling Methodology
IMV: integrated motivational volitional
NHS: National Health Service
PHQ-9: Patient Health Questionnaire
PSQI: Pittsburgh Sleep Quality Index
SCI: Sleep Condition Indicator
SIB: suicidal ideation and behavior
WLT: West London National Health Service Trust

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Proposal

Life Course Digital Twins–Intelligent Monitoring for Early and Continuous Intervention and Prevention (LifeTIME): Proposal for a Retrospective Cohort Study

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Abstract

Background: Multimorbidity, which is associated with significant negative outcomes for individuals and health care systems, is increasing in the United Kingdom. However, there is a lack of knowledge about the risk factors (including health, behavior, and environment) for multimorbidity over time. An interdisciplinary approach is essential, as data science, artificial intelligence, and engineering concepts (digital twins) can identify key risk factors throughout the life course, potentially enabling personalized simulation of life-course risk for the development of multimorbidity. Predicting the risk of developing clusters of health conditions before they occur would add clinical value by enabling targeted early preventive interventions, advancing personalized care to improve outcomes, and reducing the burden on health care systems.

Objective: This study aims to identify key risk factors that predict multimorbidity throughout the life course by developing an intelligent agent using digital twins so that early interventions can be delivered to improve health outcomes. The objectives of this study are to identify key predictors of lifetime risk of multimorbidity, create a series of simulated computational digital twins that predict risk levels for specific clusters of factors, and test the feasibility of the system.

Methods: This study will use machine learning to develop digital twins by identifying key risk factors throughout the life course that predict the risk of later multimorbidity. The first stage of the development will be the training of a base predictive model. Data from the National Child Development Study, the North West London Integrated Care Record, the Clinical Practice Research Datalink, and Cerner's Real World Data will be split into subsets for training and validation, which will be done following the k-fold cross-validation procedure and assessed with the Prediction Model Risk of Bias Assessment Tool (PROBAST). In addition, 2 data sets—the Early-Life Data Cross-linkage in Research study and the Children and Young People's Health Partnership

randomized controlled trial—will be used to develop a series of digital twin personas that simulate clusters of factors to predict different risk levels of developing multimorbidity.

Results: The expected results are a validated model, a series of digital twin personas, and a proof-of-concept assessment.

Conclusions: Digital twins could provide an individualized early warning system that predicts the risk of future health conditions and recommends the most effective intervention to minimize that risk. These insights could significantly improve an individual's quality of life and healthy life expectancy and reduce population-level health burdens.

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KEYWORDS

artificial intelligence; machine learning; mulitmorbidity; mental health; health care; AI; outcome; NCDS; national child development study

Introduction

Background

Multimorbidity, the co-occurrence of 2 or more long-term conditions, has been associated with numerous adverse outcomes and overwhelming financial burdens on health care systems [1]. Its prevalence in the United Kingdom is projected to almost double by 2035, and at least two-thirds of the gain in life expectancy for people aged >65 years will be spent with 4 or more chronic conditions [2]. Multimorbidity is most common in older people, but it is seen in patients of all ages [3]. It is more prevalent, and at younger ages, among people who live in socioeconomically deprived areas [4]. Health, behavioral, and environmental factors significantly influence individuals' risk and many processes that lead to multimorbidity begin with chronic illness at much earlier ages. Multimorbidity can occur in clusters with predictable disease pathways [5]; however, the specialization of health care has created a challenge for identifying and treating co-occurring health conditions. An interdisciplinary approach combining clinical knowledge of disease pathways, clusters, and risk factors with artificial intelligence (AI) technology could improve understanding of the biosocial factors that are associated with developing multimorbidity. Understanding key risk factors for multimorbidity could enable doctors to monitor and treat patients more effectively, potentially mitigating or preventing multimorbidity.

Rationale

A holistic, patient-centered system will be essential to address the challenge of preventing and managing multimorbidity and will require a combination of prediction, monitoring, and intervention. Digital twins—an engineering concept that uses real-world data and AI to provide a virtual representation of a physical counterpart—are starting to be explored in health care. The concept of the digital twin can be interpreted in relation to patients as a means of improving diagnostics and treatments by processing vast amounts of data to develop predictive health trajectories for individuals [6]. Our aim is to adapt this engineering solution to draw on continuously updated individual data on factors and health outcomes to simulate an individual's future health status [7].

There is little established evidence on effective means of identifying risk factors or preventing and managing multimorbidity throughout the life course [8,9]. The vast majority of multimorbidity studies aim to identify disease clusters at a single point in time, providing little information about how multimorbidity develops over time within individuals [10]. This study will develop a system where innovative AI approaches are used to analyze complex longitudinal data and predict risk levels of multimorbidity. Using simulation, digital twins could identify key risk factors, consider weaknesses in source data through quantified underreporting, model potential adverse health outcomes, and recommend the most effective intervention when given adequate information. The use of digital twins is aimed at making significant enhancements within health care and advancing knowledge of disease [6]. When used in conjunction with clinician experience and knowledge, it will aid decision-making and highlight risk factors early on, so that steps can be taken to mitigate them and avoid later health consequences. The proposed digital twin solution has the potential to have a significant positive impact on individuals and health care systems.

Aim, Hypothesis, and Objectives

The aim of this study is to identify key risk factors that predict multimorbidity throughout the life course by developing an intelligent agent using digital twins. The hypothesis is that this intelligent agent can use a wide range of biosocial variables (including physical and mental health and behavioral, socioeconomic, relational, and environmental conditions throughout an individual's life) to predict risk of multimorbidity.

The three main objectives of the Life Course Digital Twins–Intelligent Monitoring for Early and Continuous Intervention and Prevention (LifeTIME) study are the following:

1. Identify key indicators that most accurately predict lifetime risk of developing multimorbidity.
2. Implement AI via a digital twin to simulate factors impacting people throughout their life to identify when they are at risk of later developing multimorbidity, enabling early, preventive interventions based on the critical indicators collected through patient-generated monitoring and medical records.
3. Evaluate the feasibility of the digital twin system by assessing the validity and performance of the predictive model.

Methods

Study Design

Using an implementation science theoretical framework and a retrospective cohort design, this will be a feasibility study aiming to address the following research question: Can historical data and data captured via a dynamic remote monitoring system be used to develop a digital twin that can predict individual risk of developing multimorbidity over a lifetime? An implementation science framework provides guidance regarding design and conduct to translate innovative ideas into practice [11]. It also gives ideas and suggestions to achieve various intended research pursuits.

For this study, 4 longitudinal databases will be used to determine how the presence or absence of particular factors (health, behavioral, and environmental) during childhood is associated with the development of health conditions and multimorbidity over the life course. The longitudinal data are needed to inform the model about childhood factors and health outcomes over the life course to identify potential early predictors of later multimorbidity. The study will consist of two phases: (1) prototype development, where the model will be trained to identify associations using subsets of the data sets; and (2) validation, where the model will be tested on the remaining subsets. Textbox 1 and Figure 1 provide an overview of the study design and framework.

Textbox 1. Population, Intervention, Comparator, and Outcomes (PICO) framework.

Population

- Data for system development will be drawn from all age groups

Intervention

- An intelligent agent using digital twins that includes a dynamic remote monitoring system and a general predictive model

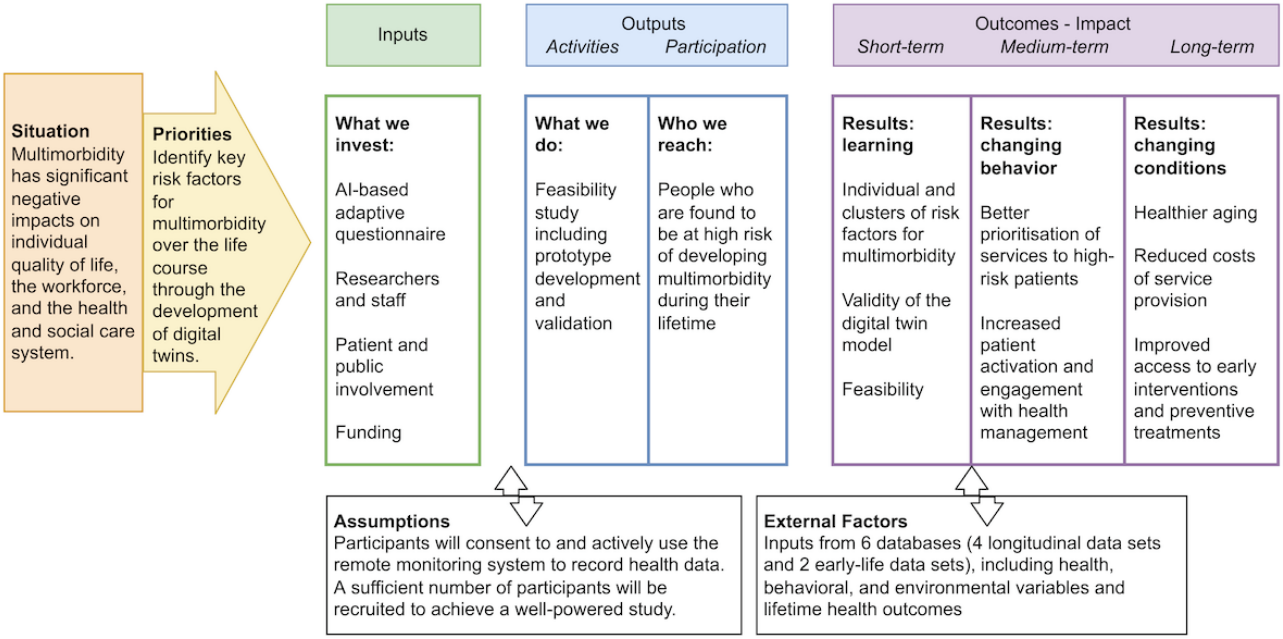
Comparator

- Real-world evidence via longitudinal data collected from databases will provide a means of validating the predictions made by the model

Outcomes

- Predicted risk of developing health conditions and multimorbidity over the lifetime

Figure 1. Life Course Digital Twins–Intelligent Monitoring for Early and Continuous Intervention and Prevention (LifeTIME) study logic diagram. AI: artificial intelligence.



Data Collection

The health care data that will be used to train and validate the model will be collected from several pre-established databases. To satisfy the data requirements of model training and validation, a few longitudinal data sets will be used and a variety of factors—including mental and physical health, and behavioral, environmental, and socioeconomic indicators—will be examined. The cohort used to train and validate the model will be built using data from previously established databases and split into random subsets. It will build upon previous work conducted on data linkage, the harmonization of multiple sources of patient-related e-records [12], and use of AI for health data analytics [13,14]. Using multiple databases will allow for a

broader range of variables to be included in model development. In total, 4 longitudinal databases (the National Child Development Study [NCDS] [15], the Clinical Practice Research Datalink [CPRD] [16,17], the North West London Integrated Care Record [NWL ICR] [18], and Cerner's Real-World Data from UK and Irish population [19]) were selected because they cover a range of mental and physical health outcomes, health behaviors, and other characteristics over decades in a diverse UK population (see Table 1).

Table 1. Characteristics of databases that will be used for model training and validation.

Database	Starting year	Number of patients	Location	Included data
National Child Development Study [15]	1958	17,415	England, Scotland, and Wales	Physical and educational development, economic circumstances, employment, family life, health behavior, well-being, social participation, and attitudes
Clinical Practice Research Datalink GOLD and Aurum [16,17]	GOLD: 1987; Aurum: 1995	GOLD: >11 million; Aurum: >19 million	GOLD: United Kingdom; Aurum: England (and Northern Ireland starting 2019)	Demographics, diagnoses, symptoms, signs, prescriptions, referrals, immunizations, behavioral and lifestyle factors, and tests
North West London Integrated Care Record Discover-NOW [18]	2015	>2.3 million	North West London	Data from all care settings (primary care, acute, mental health, community, and social care), for all disease areas
Cerner's Real-World Data [19]	—[a]	~20 million	United Kingdom (30 trusts) and Ireland (7 hospitals)	Data recorded in electronic patient records

[a]Not available.

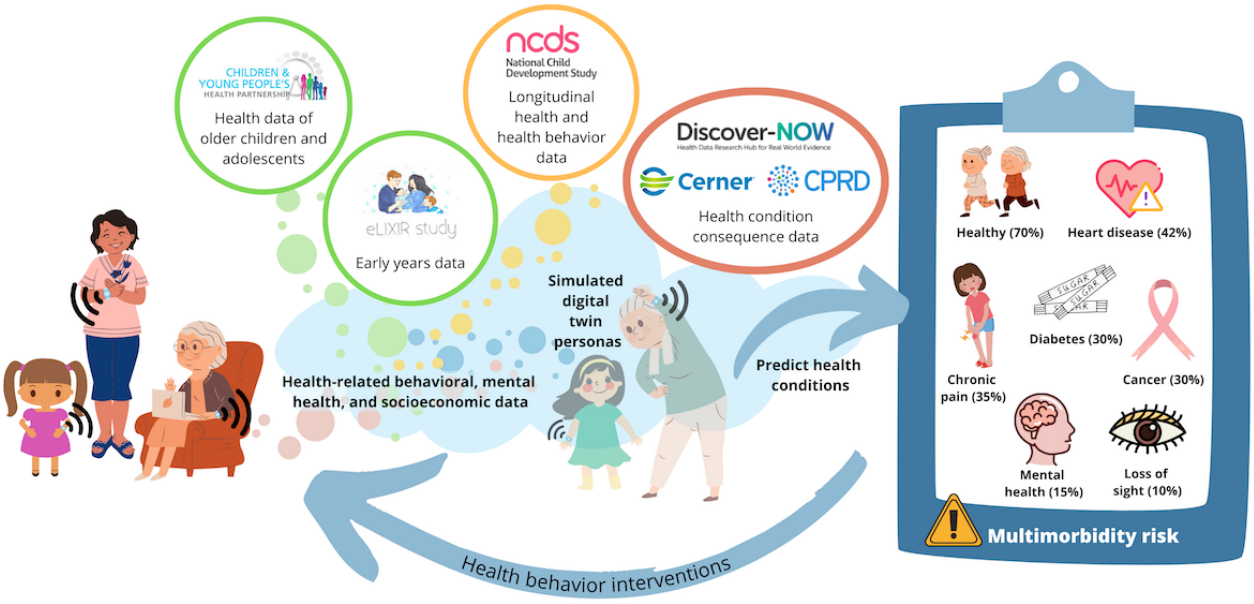
Model and Digital Twin Development

Vast amounts of data will be used to develop the data sets, which will then generate a computational model to establish the relationship between biosocial factors and later health outcomes. Machine learning will be used to train a model using a variety of factors. The model will need to be trained on longitudinal data that includes both biosocial characteristics and later health conditions to establish links between factors and outcomes and account for historical differences in risk factor and multimorbidity prevalence.

Once the predictive model has been developed based on the 4 longitudinal databases detailed in Table 1, two additional data sets will be incorporated into the development of the digital twins. Data from the Early-Life Data Cross-linkage in Research (eLIXIR) study [20] and the Children and Young People's Health Partnership (CYPHP) randomized controlled trial [21] will be included in the development of the digital twins because they track early life variables and use of health care services. Using the preliminary model developed from the longitudinal data sets in combination with machine learning to identify clusters of factors that best predict the later risk of developing multimorbidity, a series of digital twin personas will be created to provide simulations of different types of people (see Figure 2).

Although the 2 additional data sets do not contain longitudinal health outcomes, incorporating them at this stage will enable the digital twin personas to be developed based on the clustering of a more comprehensive set of variables. For instance, if a particular variable was identified in the model as a predictor of multimorbidity, these additional data sets can provide more detail about variables that commonly co-occur with that predictor. This is beneficial because these data sets will provide more current data about early life factors than the longitudinal databases. The number of digital twin personas developed will depend on the clustering of the predictive factors. For this study, these personas will be developed to represent children, but in the long term, they will be developed to simulate different stages throughout life.

Figure 2. Life Course Digital Twins–Intelligent Monitoring for Early and Continuous Intervention and Prevention (LifeTIME) overview.



Evaluation

The validity of the developed model and the digital twin prototypes will be assessed using the k-fold cross-validation procedure [22], with k being determined when the total cohort size is known. The machine learning algorithms will be tested on the validation data set to determine which model has the best fit. Model validity will be examined using a variety of indicators, including receiver operating characteristic and precision-recall curves (see Table 2). The Prediction Model Risk of Bias Assessment Tool (PROBAST) will be used to assess the model's risk of bias [23].

Table 2. Primary and secondary objectives and outcomes.

Objective	Primary outcome	Secondary outcome
Identify key indicators that most accurately predict lifetime risk of multimorbidity	Risk factors for multimorbidity	N/A[a]
Assess the validity of a model that identifies variables and predicts lifetime risk of developing multimorbidity	Validity	Risk of bias

[a]N/A: not applicable.

Ethics

Ethical approval for this study will be sought from the University of Plymouth's Faculty of Health Research Ethics and Integrity Committee. All the data being used in this proof-of-concept study will be procured from pre-existing databases. Therefore, all data access will be dependent on the approval of the study protocol by the data controllers for those databases; for instance, the CPRD database requires that study protocols be approved by an Independent Scientific Advisory Committee before data are shared. All storage and use of the data provided will comply with database-specific and General Data Protection Regulation (GDPR) requirements. It will be confirmed before access that the data have been sufficiently anonymized to comply with GDPR requirements and that the databases' patient consent processes extend to cover the sharing of anonymized data for other research purposes (ie, that their personal health data is being used in a way that could be reasonably expected by the participants). Processes for the removal of patient data—at their request to the specific database—will be established before data use with each of the database managers. Potential ethical issues relating to the development and implementation of digital twins in health care will be identified from the literature and discussions with a patient and public steering group.

Results

The study is expected to produce a validated model of the factors associated with later development of mental health conditions and multimorbidity and a series of digital personas based on that model. The results collected will inform assessments of the feasibility of pursuing further development and evaluation of the digital twin system; if unfeasible in its current state, the findings will inform understanding of problems and iterative development. This study is a starting point; the results will provide data to inform a base model that will be used in later studies, where the model will be trained and developed using remote monitoring of and data collection from real patients in combination with population health data to more closely personalize the digital twins.

Discussion

Overview

By associating a patient with a digital twin persona and then personalizing it with their evolving data, health care providers and researchers could receive a personalized risk score representing the probability that the patient will develop further health complications. With the capability to start at a young age, a digital twin system has the potential to provide significant clinical value by identifying risk factors early, so that preventive interventions can be made to reduce an individual's risk of developing long-term health conditions. This would save time and resources for health care providers, hospitals, and health care systems and reduce health problems and related financial costs for patients.

Future Directions

If the study results are positive, future research could develop and incorporate a remote monitoring system that can collect and collate individual data with the population data in a pilot trial. This would enable the digital twins to be further developed and iteratively improved based on feedback from the participants. As the system will use sensitive personal data and have ethical implications, safety and efficacy data will be an essential next step on the path to achieving wide-scale patient benefit.

Based on a user's personal data, health care providers and researchers would be able to associate an individual patient with the digital twin persona that is the best fit for them. This will then provide a risk score representing the probability that the patient will develop further complications or health conditions. In the future, the digital twin will also be trained with data on interventions so that it can provide recommendations to health care providers about what interventions are most likely to be effective for that individual. In the long term, data collected from this remote monitoring system will be combined with childhood digital twin personas to increase the variables for prediction and to personalize the best-fitting persona based on individual health data.

Limitations

Potential limitations of the study have been identified, with plans for their mitigation, to maximize the potential usefulness of the study.

1. Data linkage: The data sets used in the study are from a variety of databases that were not designed to be integrated and were not collected from the same populations. This will be mitigated by the experience of the research team and the use of machine learning techniques to aggregate a large amount of data.
2. Data quality: Understanding the errors in data is key to making predictions. This can be more difficult to quantify for survey data (particularly subjective questions) than for technical medical data. This will be mitigated by collecting data from multiple sources with large sample sizes and by prioritizing the inclusion of validated questionnaires in future remote monitoring systems.
3. Lack of individualization: Developing a model based on pre-existing data sets that do not all follow specific individuals means that there is a risk that the "digital twins" will only be a predictive model. This will be mitigated by the future development of a novel and linked system of collecting remote monitoring and sensing data that can be incorporated into digital twin personas.

Conclusion

Incorporating a remote monitoring system would enable tracking of ongoing lifestyle data, which could be combined with the individual's personal health data and population health and lifestyle data to potentially increase the potential impact. Personalized patient simulations could be used to optimize prevention or treatment selection, saving patients unnecessary side effects, reducing the number of treatments attempted, and reducing the need for repeat hospital visits. Prevention and early intervention to manage multimorbidity will support healthy aging and reduce its negative impacts on quality of life and the workforce.

Acknowledgments

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Authors' Contributions

MMI and EM conceived of the study topic and designed and drafted the protocol. LKF, AK, DW, MHvV, JM, IW, and TH contributed to the revision of the protocol. Final revision was conducted by EM.

Conflicts of Interest

EM is the Editor-in-Chief of *JMIRx Med*. All other authors declare no conflicts of interest.

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Abbreviations

AI: artificial intelligence
CPRD: Clinical Practice Research Datalink
CYPHP: Children and Young People's Health Partnership
eLIXIR: Early-Life Data Cross-linkage in Research
GDPR: General Data Protection Regulation
LifeTIME: Life Course Digital Twins—Intelligent Monitoring for Early and Continuous Intervention and Prevention
NCDS: National Child Development Study
NWL ICR: North West London Integrated Care Record
PROBAST: Prediction Model Risk of Bias Assessment Tool

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Protocol

An Agreement of Antigen Tests on Oral Pharyngeal Swabs or Less Invasive Testing With Reverse Transcription Polymerase Chain Reaction for Detecting SARS-CoV-2 in Adults: Protocol for a Prospective Nationwide Observational Study

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Abstract

Background: The SARS-CoV-2 pandemic has resulted in an unprecedented level of worldwide testing for epidemiologic and diagnostic purposes, and due to the extreme need for tests, the gold-standard Reverse Transcription Polymerase Chain Reaction (RT-PCR) testing capacity has been unable to meet the overall worldwide testing demand. Consequently, although the current literature has shown the sensitivity of rapid antigen tests (RATs) to be inferior to RT-PCR, RATs have been implemented on a large scale without solid data on performance.

Objective: This study will compare analytical and clinical sensitivities and specificities of 50 lateral flow– or laboratory-based RATs and 3 strand invasion–based amplification (SIBA)-RT-PCR tests from 30 manufacturers to RT-PCR testing of samples obtained from the deep oropharynx. In addition, the study will compare sensitivities and specificities of the included RATs as well as RT-PCR on clinical samples obtained from the deep oropharynx, the anterior nasal cavity, saliva, the deep nasopharynx, and expired air to RT-PCR on deep oropharyngeal samples.

Methods: In the prospective part of the study, 200 individuals found SARS-CoV-2 positive and 200 individuals found SARS-CoV-2 negative by routine RT-PCR testing will be retested with each RAT, applying RT-PCR as the reference method. In the retrospective part of the study, 304 deep oropharyngeal cavity swabs divided into 4 groups based on RT-PCR quantification cycle (Cq) levels will be tested with each RAT.

Results: The results will be reported in several papers with different aims. The first paper will report retrospective (analytical sensitivity, overall and stratified into different Cq range groups) and prospective (clinical sensitivity) data for RATs, with RT-PCR as the reference method. The second paper will report results for RAT based on anatomical sampling location. The third paper will compare different anatomical sampling locations by RT-PCR testing. The fourth paper will focus on RATs that rely on central laboratory testing. Tests from 4 different manufacturers will be compared for analytical performance data on retrospective deep oropharyngeal swab samples. The fifth paper will report the results of 4 RATs applied both as professional use and as self-tests. The last paper will report the results from 2 breath tests in the study. A comparison of sensitivity and specificity between RATs will be conducted using the McNemar test for paired samples and the chi-squared test for unpaired samples. Comparison of the positive predictive value (PPV) and negative predictive value (NPV) between RATs will be performed by the bootstrap test, and 95% CIs for sensitivity, specificity, PPV, and NPV will be calculated as bootstrap CIs.

Conclusions: The study will compare the sensitivities of a large number of RATs for SARS-CoV-2 to with those of RT-PCR and will address whether lateral flow–based RATs differ significantly from laboratory-based RATs. The anatomical test locations for both RATs and RT-PCR will also be compared.

Trial Registration: ClinicalTrials.gov NCT04913116; https://clinicaltrials.gov/ct2/show/NCT04913116

International Registered Report Identifier (IRRID): DERR1-10.2196/35706

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KEYWORDS

SARS-CoV-2; COVID-19; point of care; PoC; antigen test; anatomic sampling location; Reverse Transcription Polymerase Chain Reaction; RT-PCR; rapid antigen test; RAT; testing; antigen; sampling; PCR; rapid; protocol; prospective; observational; agreement; oral; adult; sensitivity; specificity; test location; anatomy; saliva; swab; nasopharyngeal; nasal

Introduction

Background

The SARS-CoV-2 pandemic has resulted in an unprecedented level of worldwide testing for epidemiologic and diagnostic purposes. In Denmark, at the peak of testing activity in week 20 in 2021, a total of 615,000 individuals (10.6% of the total population of 5.8 million) were tested daily by Reverse Transcription Polymerase Chain Reaction (RT-PCR) or rapid antigen tests (RATs). PCR and PCR-like technologies (nucleic acid amplification technologies [NAATs]) are considered the gold standard for detection of viral pathogens, but due to the extreme need for tests, the national RT-PCR testing capacity was unable to meet the overall testing demand. Consequently, RATs, which may be performed by non-health-care-trained individuals outside of health care facilities with results within minutes, were implemented on a large scale. At the peak testing level, 440,000 RATs were performed daily in Denmark compared to 175,000 RT-PCR tests. This may be problematic, however, as unlike RT-PCR tests, which are clinically validated, the only information available about the sensitivity of a specific RAT is most often the manufacturer's instructions for use (IFU).

Previous Experience With RATs for Infectious Diseases

Prior to the SARS-CoV-2 pandemic, commercially available RATs were primarily based on the lateral flow immunoassay principle first described by Leuvering et al [1] in 1980 and are available for a number of pathogens [2]; especially point-of-care (PoC) assays for detection of malaria [3,4], group A streptococcus [5], respiratory syncytial virus [6,7] and influenza virus types A and B [7,8] have been widely implemented. In a meta-analysis describing the performance of rapid diagnostic tests for group A streptococcal pharyngitis [5], lanthanide immunofluorescent assay (LIFA) and optical immunoassay (OIA) were performing similarly when individual studies were pooled with an average sensitivity of 85% and an average specificity of 97% against culture, but the assays performed with large differences between different suppliers. The sensitivity varied from 71% to 95%, and the specificity varied from 62% to 100% [9-11]. In a meta-analysis published by Chartrand et al [8] describing the performance of rapid diagnostic tests for influenza virus, in 67 studies where RT-PCR was the comparator, a pooled sensitivity of 54% and a pooled specificity of 99% were reported. A significantly higher sensitivity was reported in studies showing results from children compared to studies reporting results from adults. In a meta-analysis published by Merckx et al [7], 94 studies on influenza A and 30 studies on influenza B applying traditional lateral-flow technology compared to RT-PCR showed a pooled sensitivity of 54.4% for influenza A and 53.2% for influenza B and a pooled specificity of 99.4% for influenza A and 99.8% for influenza B. When newer digital immunoassays were applied (18 studies on influenza A and 17 studies on influenza B), a pooled sensitivity of 80.0% for influenza A and 76.8% for influenza B and a pooled specificity of 98.3% for influenza A and 98.7% for influenza B were reported. Again, assays performed on children showed a significantly higher sensitivity compared to assays performed on adults. In a meta-analysis published by Bruning et al [6], 134 studies on influenza and 32 studies on respiratory syncytial virus applying rapid immunoassays compared to RT-PCR showed a pooled sensitivity of 61.1% and a pooled specificity of 98.8% for influenza. For respiratory syncytial virus, the pooled sensitivity was higher (75.3%) and the pooled specificity was 98.7% [6]. The authors reported huge differences between different commercial influenza assays (ie, 36% for Directigen Flu A+B [BD Diagnostic Systems] and 44% for QuickVue Influenza A+B [Quidel] and BinaxNow Influenza A&B [Alere] to 75% for Sofia Influenza A+B [Quidel] and 76% for mariPOC [ArcDia International]). However, for respiratory syncytial virus, the difference in sensitivity between the reported assays was not significant.

Background on RATs for SARS-CoV-2

Thus, prior to the SARS-CoV-2 pandemic, all available PoC immunoassays for other pathogens have shown inferior performance compared to NAATs [5-8]. Immunoassays in general show excellent specificity but inferior sensitivity and should, for diagnostic purposes, be used as rule-in assays only [12,13]. Early in the SARS-CoV-2 pandemic, RATs based on lateral-flow technology were made commercially available, and new commercial RATs for detection of SARS-CoV-2 are continuously being introduced. The literature on analytical as well as clinical sensitivity is scarce; most often, a single RAT is compared against a NAAT. The sensitivity of individual RATs varies according to population (eg, symptomatic vs nonsymptomatic) and timing related to symptoms (if any) [14] and may be as low as 37.7%. Interestingly, according to the manufacturers' own reported data, 125 commercial tests all had a clinical sensitivity of >80.6% (range 80.6%-100%, average 95.69%, median 96.17%) [15]. Of the 125 tests, 121 (99.2%)

had a sensitivity of >90% according to the manufacturers' own reported data.

Considering the extreme number of worldwide performed RATs, the lack of thorough comparisons of the performances of different RATs is problematic, as decision makers have so far spent large amounts of financial resources based on limited objective and validated data.

Research Aims

In this study, we will compare the analytical as well as the clinical sensitivities and specificities of 50 RATs and 3 strand invasion–based amplification (SIBA)-RT-PCR tests from 30 manufacturers to RT-PCR on deep oropharyngeal samples, which is the chosen anatomical sampling site for routine SARS-CoV-2 RT-PCR in Denmark. In addition, we will compare the clinical sensitivities and specificities of all included RATs as well as RT-PCR on clinical samples obtained from the deep oropharyngeal cavity, the anterior nasal cavity, saliva, the deep nasopharyngeal cavity, and expired air to RT-PCR on deep oropharyngeal samples.

Methods

Summary of Design

This research combines a retrospective study of analytical sensitivity and specificity with a prospective accuracy observational study. In the prospective part of the study, approximately 200 individuals testing positive for SARS-CoV-2 and 200 individuals testing negative for SARS-CoV-2 by routine SARS-CoV-2 testing will be subsequently retested with each RAT, with RT-PCR on deep oropharyngeal cavity swabs as the reference method.

In the retrospective part of the study, 304 deep oropharyngeal cavity swabs stored in Universal Transport Medium (UTM; Copan Diagnostics Inc, Brescia, Italy) will be divided into 4 groups based on RT-PCR quantification cycle (C_q) levels and tested with each included RAT.

Recruitment

Individuals who test positive for SARS-CoV-2 by a public test provider, either TestCenter Denmark (TCDK; national complimentary screening for SARS-CoV-2) or a regional department of clinical microbiology (DCM; health care workers, residents at nursing homes, outpatients, individuals undergoing elective surgery, and hospitalized patients) will be identified directly in the local microbiology laboratory information systems. SARS-CoV-2-positive individuals will be invited to participate in the study either by phone or by email. Twice daily (approximately at 8:30 AM and 8:30 PM), all individuals who have tested positive within the past 12 h and live in a geographic area in which the project includes patients will be invited by secure public email (e-Boks) to participate in the study and asked to contact a test coordinator by email or phone within 24 h. Each SARS-CoV-2-positive individual will be asked to provide information about the test date, current address, and contact information to allow the test coordinator to plan the new testing in the individual's private home by an outpatient testing team. All individuals will be retested within 72 h after the first initial positive test for SARS-CoV-2.

Data Management

Written consent for participation and collection of data in the study will be collected at the test center. For consecutive samples, each RAT and the sample for RT-PCR will be marked with a local sample identifier number and data will be paired according to this sample identification number. Individuals who test positive for SARS-CoV-2 will be invited by email or phone to participate in additional testing. The number of individuals invited to participate will be registered, without any additional information. For additional testing, a new sample identifier number will be used to pair the new swab(s) for RT-PCR testing and RATs conducted by the outpatient team. Data, including photodocumentation of all RAT results, will be sent to the steering group and stored in a secure regional electronic file archive.

When retested by the outpatient testing team, a signed consent form for participation will be collected and no other information about the participating individual will be stored afterward. SARS-CoV-2-positive and SARS-CoV-2-negative individuals will be included until approximately 200 RT-PCR-positive and RT-PCR-negative individuals have been included for each RAT.

Data Validation

The results of all RATs will be documented by picture, and all results will subsequently be reviewed by the test coordinator. The test coordinator will inspect all pictures and change negative results to positive if a visual target band is present on the pictures of the RAT. If the target band cannot be verified, the original interpretation by the outpatient testing team will be sustained, as the outpatient testing team will get the opportunity to see the test from multiple angels and thereby to detect the sample band on the RAT, whereas the test coordinator is limited by review of the picture documentation. For RT-PCR results, all samples negative for SARS-CoV-2 and a human control gene will be considered inconclusive and curves will be inspected by RT-PCR staff a second time to ensure that results are reported correctly.

Sampling and RATs

Participating individuals will be tested by RATs as well as RT-PCR on clinical samples obtained from the anterior nasal cavity, the deep oropharyngeal cavity, saliva, the deep nasopharyngeal cavity, and expired air. Sampling for RATs will be performed using the sterile swabs provided by each manufacturer and will be executed according to the instructions from the manufacturer. If no special instructions are provided and for RT-PCR, samples will be collected as specified next. By default, RATs will be performed on deep oropharyngeal cavity swabs, as deep nasopharyngeal cavity swabbing is not recommended in Denmark due to the discomfort for the individual being tested. In addition to deep oropharyngeal cavity testing, manufacturers could submit their RATs for testing on other sample material, such as swabs from the anterior nasal cavity, saliva, or expired air.

Each RAT will be executed as instructed by the manufacturer in the IFU. When non-CE marked sample materials are used, sampling will be conducted as instructed by the manufacturer using swabs and sampling media delivered specifically by the manufacturer. All RATs will be performed on-site immediately after sample collection. The results will be collected on a test chart, and a photo will be taken of the RAT for documentation of results. Self-tests will be performed by the tested individuals themselves 2 h following the sampling procedure performed by the outpatient sampling team. For self-testing, tested individuals will be asked to send a picture of the test strip, together with their interpretation of the test result to the test coordinator.

Anterior Nasal Cavity Swabs

Up to 3 sterile swabs will be inserted into the anterior nasal cavity at a time. The swabs will be inserted 2-3 cm from the nostril, aiming below the inferior turbinate, and rotated 5 times in each nostril to collect sample material. Swabs for RATs will be tested immediately after sample collection, whereas sterile flocked nylon swabs for RT-PCR will be transferred to a NEST disposable sampler inactivation transport medium (NEST tube and Scientific Nasopharyngeal Specimen Collection Swab, Wuxi NEST Biotechnology Co., Ltd, Wuxi City, Jiangsu Province, China) and sent for RT-PCR.

Deep Nasopharyngeal Cavity Swabs

Samples for deep nasopharyngeal cavity testing will be collected only for RT-PCR to compare anatomical testing locations. A sterile flocked nylon swab (NEST Scientific Nasopharyngeal Specimen Collection Swab, cat. no. 202004) with 1 break point at 8 cm will be inserted below the inferior turbinate until it reaches the posterior nasopharyngeal wall. The swab will be rotated 5 times, and the collected sample material will be transferred to a NEST tube and sent for RT-PCR.

Deep Oropharyngeal Cavity Swabs

Testing will be conducted with 3 oropharyngeal swabs at a time in a tree point swab procedure. The 3 swabs will be held together and rotated at both sides of the palatoglossal arch and the posterior wall of the oropharynx. The tongue or teeth will be avoided, and all 3 areas will need to be sampled. Of the 3 swabs, 2 will be tested immediately by RATs, whereas the third flocked nylon swab will be sent for RT-PCR in a NEST tube (Oropharyngeal Specimen Collection Swab, cat. no. 202003, Wuxi NEST Biotechnology Co, Ltd).

Saliva Sample Collection

Saliva samples will be collected according to the manufacturer's instructions. If no specific instruction is provided or for RT-PCR, the sample will be collected by instructing the person being tested to massage the glands on both sides of the jaw and them sampling the saliva produced from the parotid, submandibular, and sublingual glands. Tested persons will be instructed to place the tongue on the hard palate and bow the head forward to let saliva be secreted naturally into a plastic cup/saliva collector tube while massaging. Saliva for RT-PCR will be collected in a NEST Scientific Saliva Collection Kit with inactivating transport media (cat. no. 203011).

Expired Air Collection

Collection of expired air will be performed according to the manufacturer's instructions and will be described in detail when the results are reported. Results will be recorded from 2 different tests on expired air.

RT-PCR Testing at the Danish Technology University

Participants in the prospective part of the study will be either retested after invitation or tested as part of surveillance/diagnostics for SARS-CoV-2. A sample from the latter group will be locally tested at the local DCM or sent to the TCDK for RT-PCR. For all participants, an oropharyngeal sample in a NEST tube will be sent to the test center at Technical University of Denmark (DTU), Lyngby, to ensure that all participating individuals are tested similarly, and all RATs will be compared to the same reference RT-PCR. To evaluate the anatomical testing site for RT-PCR, additional samples will be obtained from the deep nasopharyngeal cavity, the anterior nasal cavity, the deep oropharyngeal cavity, and saliva in NEST tubes and sent to the DTU for RT-PCR testing.

At the DTU test center, all samples will be tested for SARS-CoV-2 by applying the CoviDetect – COVID-19 Multiplex RT-PCR assay from PentaBase (PentaBase APS, Odense, Denmark). In short, samples will be received in NEST tubes (3 M guanidine thiocyanate buffer for instant viral lysis). Viral RNA will be purified from a 200 µL sample on a Beckman Coulter Biomek i7 (Beckman Coulter Life Sciences, Indianapolis, NV, USA) with magnetic bead–based purification (RNAadvance Viral XP kit, Beckman Coulter, Indianapolis, NV, USA) with a 30 µL eluate. Next, 5 µL of the purified RNA sample will be mixed with 10 µL of 2x Mastermix One Step PrimeScript III, RT-PCR mix (cat. no. RR600; TaKaRa Bio Europe AB, Göteborg, Sweden) and 5 µL of the 4x primer-probe mix. The assay includes 2 targets in the nucleocapsid protein gene (N-gene) of SARS-CoV-2 and 1 target for the human RNase P gene (RP-gene) as a process control and to confirm the presence of human DNA in the sample (Table 1).

Samples will be amplified by a 2-step touch-down RT-PCR program on a Rotor_Gene (Qiagen Aarhus, Aarhus, Denmark) with reverse transcription at 52°C for 5 min, initial PCR activation at 95°C for 10 s, 7 cycles of denaturation at 95°C for 5 s with annealing/elongation at 66°C for 30 s, and finally 38 cycles of denaturation at 95°C for 5 s and 60°C for 30 s.

Table 1. Primer and probe sequences for the 2 N-gene[a] targets included in the CoviDetect multiplex assay. Sequences for the human RP-gene[b] (marked with Cy5[c]) or concentrations are not reported by the manufacture.

Oligonucleotide name	Sequence (5'-3')
N1 forward primer	GACCCCAAAATCAGCGAAAT
N1 reverse primer	CGCAGTATTATTGGGTAAACC
N1 probe (5'-FAM[d]/3'-unknown)	ACCCCGCATTACGTTTGGTGGACC
N2 forward primer	AGGAACTGATTACAAACATTGGC
N2 reverse primer	TGTAGGTCAACCACGTTCCC
N2 probe (5'-HEX[e]/3'-unknown)	TGCACAATTTGCCCCAGCG

[a]RP-gene: RNase P gene.

[b]N-gene: nucleocapsid protein gene.

[c]Cy5: cyanine fluorophore.

[d]FAM: 6-carboxyfluorescein fluorophore.

[e]HEX: hexachloro-fluorescein fluorophore.

RT-PCR at the TCDK

To evaluate whether the anatomical test location is independent of the RT-PCR of choice and test media, all samples for comparison of anatomical locations will be sent to the TCDK for repeated RT-PCR testing. Additional samples will be collected from the deep oropharyngeal cavity, the anterior nasal cavity, and saliva. Deep oropharyngeal cavity and anterior nasal cavity swabbing will be conducted as described before. Anterior nasal cavity swabbing will be either performed as professional testing or self-administered testing under supervision. The salivary swab will be collected by placing the swab on the volunteer's tongue for 10 s without any stimulation of the salivary glands. The same type of flocked swab will be used for sample collecting from all 3 anatomical testing locations (CLASSIQSwab Sterile Dry Fiber Swabs, Copan Diagnostics Inc), and all samples will be collected in individual screw cap–sealed 1000 µL 2D barcoded tubes (LVL Technologies, Crailsheim, Germany) without stabilizing or transport media. Samples will be delivered and analyzed within 24 h of sample collection at the TCDK.

The sample material will be suspended from the swabs directly in sample tubes using a Hamilton Microlab VANTAGE (Hamilton Company, Reno, NV, USA) liquid-handling system by trained laboratory technicians. Individual swabs will be suspended in 700 µL of 1X Dulbecco's phosphate-buffered saline (DPBS; Gibco, Thermo Fischer Scientific, Waltham, MA, USA) and agitated at 700 RPM for 10 min, and 200 µL will be transferred to deep-well plates for downstream processing.

RNA extraction and purification will be carried out using a Beckman Coulter RNAdvance Blood kit on a Beckman Coulter Biomek i7 automated workstation with 200 µL sample input and 50 µL elution volume. From this, 5 µL eluate will be transferred to a 96-well skirted PCR plate.

Each PCR tube will contain 12.5 µL of Luna Universal Probe One-Step RT-PCR Kit reaction buffer, 1.25 µL of Luna WarmStart RT Enzyme mix (New England Biolabs Inc, Ipswich, MA, USA) primers and probes targeting the envelope gene (E-gene) [16] (at 100 µM, volumes and sequences in Table 2), 5 µL of the template, and DNAse/RNAse-free water for a total volume of 25 µL.

Single-target RT-PCR assays will be performed on a Bio-Rad CFX96 Touch Real-Time PCR Detection System (Bio-Rad Laboratories, Hercules, CA, USA) using the software CFX Maestro (Bio-Rad Laboratories). The cycling conditions will be reverse transcription at 55°C for 10 min and initial denaturation at 95°C for 3 min, followed by 45 cycles of denaturation and annealing/extension at 95°C for 15 s and 58°C at 30 s, respectively.

Table 2. Primers and probe sequences and final concentrations of the oligonucleotides targeting the E-gene[a] by TCDK[b] RT-PCR[c].

Oligonucleotide name	Sequence (5'-3')	Final concentration (nM)
E_Sarbeco_F	ACAGGTACGTTAATAGTTAATAGCGT	400
E_Sarbeco_R	ATATTGCAGCAGTACGCACACA	400
E_Sarbeco_P1	FAM[d]-ACACTAGCCATCCTTACTGCGCTTCG-BHQ1[e]	200

[a]E-gene: envelope gene.

[b]TCDK: TestCenter Denmark.

[c]RT-PCR: Reverse Transcription Polymerase Chain Reaction.

[d]FAM: 6-carboxyfluorescein fluorophore.

[e]BHQ1: Black Hole Quencher 1.

Retrospective Testing

Samples will be stored in UTM to ensure that they can be used for subsequent antigen testing as well as subsequent retesting by RT-PCR. We will use laboratory-developed test (LDT) RT-PCR that reports threshold cycle (C_t) values in order to be able to stratify the samples into different C_q range groups directly from aliquoted samples that will also be used for RATs.

For the retrospective study arm, stored excess material from 204 previously SARS-CoV-2-positive and 100 SARS-CoV-2-negative samples stored at –80°C will be defrosted on ice and retested by RT-PCR to verify the C_q value. Selected samples will be defrosted and adjusted with UTM (at 4°C; Copan Diagnostics Inc) or pooled as multiple negative samples, again on ice, and aliquots of 250-500 µL volume will be stored at –80°C until use.

Negative samples will be prepared from routine samples obtained from 10 individuals who test negative in routine RT-PCR. The samples will be pooled and aliquoted into 40 vials of 500 µL. Positive samples will be adjusted to a certain C_q range as either 1 part sample plus 3 parts UTM, which will be conducted for 186 samples, or as 1 part sample plus 7 parts UTM, which will be conducted for 13 samples. Of these 13 samples, 1 (8%) has a final C_q between 30 and 35, and the remaining 12 (92%) have a C_q of >35. In addition, 5 samples will be diluted as 1 part sample plus 11 parts UTM. Of these 5 samples, 1 (20%) sample has a C_q of <25 and 4 (80%) have a C_q between 25 and 30 each in our LDT RT-PCR. The final 204 samples will be stored as 50 (24.5%) positive samples with a C_q of <50, 54 (26.5%) samples with a C_q between 25 to 30, 50 (24.5%) samples with a C_q between 30 and 35, and 50 (24.5%) samples with a C_q level of >35.

For each RAT, 1 aliquot of each sample will be defrosted, and 200 µL of the sample material will be transferred to RAT lysis buffer and tested according to the manufacturer's instructions by laboratory-trained personnel; 1 aliquot will be used for each RAT, and excess material will be discharged; and 1 aliquot will be retested by RT-PCR after thawing to verify the C_q of the sample.

In short, 180 µL of the sample material will be purified on a MGISP-960 purifier with a MGIEasy Magnetic Beads Virus DNA/RNA extraction kit (MGI Tech Co, Ltd, Shenzhen, China) and a final eluate of 33 µL purified DNA/RNA. Next, 8 µL of purified RNA will be mixed with 10 µL of 2x KiCqStart One-Step Probe RT-PCR ReadyMix from Sigma-Aldrich (Merck Life Science A/S, Søborg, Denmark), 1 µL of 2'-deoxyuridine 5'-triphosphate (dUTP; 4 mM), and 1 µL of primer-probe mix targeting the E-gene and N-gene of SARS-CoV-2 and the human RP gene as process and sampling controls (Table 3) [16,17].

RT-PCR will be performed on a LineGene 9600-platform (Hangzhou Bioer Technology Co, Ltd, Hangzhou, China) with reverse transcription at 50°C for 10 min, reverse transcription inactivation/initial denaturation at 95°C for 60 s, and 45 cycles of denaturation at 95°C for 5 s, followed by annealing/elongation at 60°C for 30 s.

Table 3. Primers and probe sequences and final concentrations of the oligonucleotides targeting the E-gene[a], N-gene[b], and human RP-gene[c] by LDT[d] RT-PCR[e].

Oligonucleotide name	Sequence (5'-3')	Final concentration (nM)
E_Sarbeco_F	ACAGGTACGTTAATAGTTAATAGCGT	500
E_Sarbeco_R	ATATTGCAGCAGTACGCACACA	400
E_Sarbeco_P	LC610[f]-ACACTAGCCATCCTTACTGCGCTTCG-BBQ[g]	150
N2_CDC_F	TTACAAACATTGGCCGCAAA	400
N2_TibMol_R1	AAGGTGTGACTTCCATGCCA	400
N2_CoV2_P	FAM[h]- ACAATTTGCCCCCAGCGCTTCAG-BBQ	150
H_RnaseP_F	AGATTTGGACCTGCGAGCG	100
H_RnaseP_R	GAGCGGCTGTCTCCACAAGT	100
H_RnaseP_P	Cy5[i]- TTCTGACCTGAAGGCTCTGCGCG-BBQ	125

[a]E-gene: envelope gene.

[b]N-gene: nucleocapsid protein gene.

[c]RP-gene: RNase P gene.

[d]LDT: laboratory-developed test.

[e]RT-PCR: Reverse Transcription Polymerase Chain Reaction.

[f]LC610: LightCycler Red 610 fluorophore.

[g]BBQ: BlackBerry Quencher.

[h]FAM: 6-carboxyfluorescein fluorophore.

[i]Cy5: cyanine fluorophore.

Statistical Analysis

Prospective Study Arm

The performance of each RAT will be reported as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) compared to oropharyngeal swabs evaluated by RT-PCR. Performance of RATs will further be evaluated regarding RT-PCR results and stratified into 3 different C_q ranges as strong positive (C_q<15), intermediate positive (C_q=15-20), and weak positive (C_q>20).

Among consecutively collected prospective samples, the fraction of samples testing negative for human DNA by RT-PCR will be reported.

Retrospective Study Arm

Determination of analytical sensitivity and specificity will be stratified into 4 groups by RT-PCR (C_q=20-25, C_q=25-30, C_q=30-35, and C_q>35).

Comparison of sensitivity and specificity between RATs will be performed using the McNemar test for paired samples and the chi-squared test for unpaired samples. The level of significance will be 0.05. Comparison of the PPV and NPV between RATs will be performed using the bootstrap test.

We will calculate 95% CIs for sensitivity, specificity, PPV, and NPV as bootstrap CIs.

Data Exclusion

Patients and their RAT results will be excluded from further analysis if no oropharyngeal swab has been collected for RT-PCR or if the sample has not been sent for reference RT-PCR testing at the DTU but has only been locally analyzed at the DCM.

Ethical Approval

The study was evaluated by the National Committee on Health Research Ethics in the Danish Capital Region to be a method validation study without the need for approval by the committee (decision H-20068579). Access to test results for research was granted by the Capital Region of Denmark – Research and Innovation (R-20083753), and contact with participants without prior consent from them was granted by the board of directors at the hospitals at which the participating DCMs are situated.

Results

Summary

Results will be divided into several papers with different aims.

The first paper will report both retrospective and prospective performance data for RATs, with RT-PCR results as the reference method. The analytical performance data will be reported for 32 RATs and 1 SIBA-RT-PCR test, together with performance data from 43 RATs and 2 SIBA-RT-PCR tests from prospectively collected samples. Results will be reported overall and stratified into different C_q range groups.

The second paper will report results for RATs based on anatomical testing locations, comparing results from individuals who will be tested at multiple anatomical testing sites with the same RAT. Comparison of anatomical testing sites will be performed for 7 tests between the deep oropharyngeal cavity and the anterior nasal cavity, 3 tests between the deep oropharyngeal cavity and saliva, 2 tests between the anterior nasal cavity and saliva, and 2 tests between all 3 anatomical testing sites.

In the third paper, different anatomical testing sites will be compared for RT-PCR testing. Data from 2 different RT-PCR methods will be reported for RT-PCR from either samples collected in NEST buffer or samples collected as dry swabs. Approximately 600 SARS-CoV-2-positive and 600 SARS-CoV-2-negative individuals will be included for RT-PCR of liquid samples as deep oropharyngeal cavity swabs, anterior nasal cavity swabs, and saliva. Approximately for one-third of the individuals, deep nasopharyngeal cavity swabs will be included to allow comparison between all 4 anatomical sampling sites. In addition, approximately 400 SARS-CoV-2-positive and 100-SARS-CoV-2 negative individuals will be tested by dry deep oropharyngeal cavity swabs, anterior nasal cavity swabs, and saliva.

The fourth paper will focus on RATs that rely on central laboratory testing. Tests from 4 different manufacturers will be compared for analytical performance data on retrospective samples collected as deep oropharyngeal swabs. In addition, approximately 200 SARS-CoV-2-positive and 200 SARS-CoV-negative prospective samples will be compared for performance data from either deep oropharyngeal cavity swabs or anterior nasal cavity swabs as 1 test from either of the testing sites and 2 tests from both testing sites. In this way, 2 samples from each individual will be used for all 6 tests. Results will be compared to the results from RATs in the first paper.

In the fifth paper, 4 RATs will be tested both as professional use and as self-testing. The results from these 4 test comparisons will be reported, together with prospective performance data from 3 additional tests that will be collected as self-tests in the study.

The final paper will report the results from 2 breath tests performed in the study. Both tests will be tested on approximately 400 SARS-CoV-2-positive individuals and 200 SARS-CoV-2-negative individuals in the prospective part of the study. For 1 of the tests, the time to a positive test will be recorded and can be compared to results for the same test from deep oropharyngeal cavity swabs and anterior nasal cavity swabs.

Discussion

Summary

To the best of our knowledge, this is the largest study, both regarding the number of included tests and the number of included individuals, comparing RATs for SARS-CoV-2 on prospective samples that has been conducted so far. We will not only compare a large number of RATs but will also be able to address whether RATs as lateral-flow tests differ significantly from central laboratory–based RATs. Likewise, the anatomical test locations for both RATs and RT-PCR will be compared for

multiple RATs, thereby adding information about testing sites for RATs and RT-PCR. Finally, the study will address self-testing versus professional testing and the use of expired air for RATs.

Limitations

The study has 4 main limitations. First, as the RATs performed on participating outpatients in the prospective part of the study will be visually evaluated at the time of the test by the individual performing the test, and as this individual will be aware that the patient currently being tested by RATs has previously, within the last few days, tested positive by RT-PCR, the individual performing the test and visually evaluating the test result will be biased toward a positive result. Censoring the initial on-site visual evaluation by later evaluation of a picture will only be implemented if the initial on-site evaluation is negative and the subsequent validation by inspection of the picture by a test coordinator is positive. Initial on-site positive evaluations will not be subsequently censored by the test coordinator, as the outpatient testing team will get the opportunity to see the test strip from multiple angels, whereas the test coordinator is limited by review of the picture documentation. Thus, it is estimated that the sensitivity values obtained in the prospective part of the study will be biased toward higher sensitivity.

Second, as this study will be performed within a specific time frame at specific geographic locations in Denmark, the SARS-CoV-2 variants included in this study will reflect the variants present at that time and place and will likely not include all known variants. There are emerging data suggesting that different RATs will perform differently against different variants [18]; thus, the sensitivities for the different included RATs reported in this study may not reflect the actual sensitivity levels in future clinical test settings.

Third, the study will be performed in an unvaccinated population and vaccination toward SARS-CoV-2 may alter the sensitivity of RATs. Indeed, it has been shown that the peak virus load may be unaffected by vaccination, but vaccination can accelerate viral clearance, thereby narrowing the period for a positive RAT [19].

Finally, the study is designed to describe differences in sensitivity, both between the different RATs included and between different anatomical test sites. Although specificity values will be reported, the study is not powered to detect differences in specificity, neither between the different RATs included nor between different anatomical test sites.

Conclusion

The study will compare the sensitivities of a large number of RATs for SARS-CoV-2 with those of RT-PCR and will address whether lateral flow–based RATs differ significantly from laboratory-based RATs. The anatomical test locations for both RATs and RT-PCR will also be compared.

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Participating suppliers of rapid antigen tests (RATs) were asked to supply the necessary tests and any modifications they wished for the testing procedure, together with a participation fee of DDK 150 (USD 21.65) per 2 participating tests or anatomical test locations. The results will be presented to the participating companies at the time of submission of the paper for publication, and the participating companies will get 10 working days to comment on their own results. Their comments may be reported as supplementary data for the publication, but any change in the paper will be on the discretions of the authors. The sponsors will therefore not play any role in the planning, collection, analysis, or reporting of results.

Conflicts of Interest

None of the members of the steering committee have any financial or other competing interests in any companies providing tests to the study. Members of the writing group have been asked to declare any financial or other competing interests as part of the writing process and may be excluded if they have commercial interests in the results.

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Abbreviations

BBQ: BlackBerry Quencher
BHQ1: Black Hole Quencher 1
Cq: quantification cycle
Cy5: cyanine fluorophore
DCM: department of clinical microbiology
DTU: Technical University of Denmark
FAM: 6-carboxyfluorescein fluorophore
HEX: hexachloro-fluorescein fluorophore
IFU: instructions for use
LC610: LightCycler Red 610 fluorophore
LDT: laboratory-developed test
NAAT: nucleic acid amplification technology

PCR: polymerase chain reaction
PoC: point of care
RAT: rapid antigen test
RT-PCR: Reverse Transcription Polymerase Chain Reaction
SIBA: strand invasion–based amplification
TCDK: TestCenter Denmark
UTM: Universal Transport Medium

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Protocol

Virtual Prehabilitation in Patients With Cancer Undergoing Surgery During the COVID-19 Pandemic: Protocol for a Prospective Feasibility Study

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Abstract

Background: Since the beginning of the COVID-19 pandemic, preoperative care, also termed prehabilitation, has become increasingly relevant due to the decreasing functional and psychosocial health of patients with cancer, which is a result of the pandemic restrictions. Concurrently, access to telehealth has improved; telehealth comprises all remote care delivery facilitated by information technologies (ie, virtually).

Objective: The aim of this protocol is to describe the rationale and methodology for a major trial investigating the feasibility and safety of multimodal virtual prehabilitation services (ie, teleprehabilitation).

Methods: This single-arm feasibility trial aims to recruit 100 patients with cancer to receive teleprehabilitation throughout their preoperative period. The inclusion criteria are as follows: (1) 18 years of age or older, (2) scheduled for elective cancer surgery and referred by a surgeon, (3) medically cleared by the referring physician to engage in physical activity, and (4) have a good comprehension of the English or French language. Feasibility will be assessed by documenting recruitment, adherence, and retention rates, in addition to patients' motives for not participating in the trial, low participation, or discontinuation. The secondary outcome of safety will be assessed by reporting program-related adverse events.

Results: The Montreal General Hospital Foundation funded the project in August 2020. The protocol was then approved by the Research Ethics Board of the McGill University Health Centre in January 2021 (ID No. 2021-6730). The first patient was recruited in March 2021, and recruitment is expected to end in September 2022. As of March 2022, 36 patients have been recruited, including 24 who have completed their participation. No adverse events have been reported. Data collection is expected to conclude in November 2022. Data analysis will be performed, and the results will be published by the beginning of 2023.

Conclusions: This trial will provide guidance on the use of telehealth in the administration of prehabilitation services. The trial will provide a large amount of information that will respond to gaps in the literature, as there are minimal reports on the use of telehealth rehabilitation and prehabilitation services among elderly populations and in acute contexts, such as the preoperative period.

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KEYWORDS

prehabilitation; telehealth; functional capacity; cancer care; exercise; malnutrition; psychosocial support

Introduction

The COVID-19 pandemic prompted many health disparities globally. Notably, the World Health Organization has warned of the possible postponement or cancellation of cancer surgery and the risk of death of many patients awaiting surgery [1,2]. The potential impacts of the pandemic on both the physical and mental health of patients were previously discussed in editorials and articles [3-6]. Prehabilitation is a novel field of study, whereby the principles of rehabilitation are applied preoperatively to optimize patient health with the hope of minimizing the stress experienced with patients' surgery and the recovery that ensues. Prehabilitation is multidisciplinary and addresses modifiable risk factors by providing patients with multimodal health interventions, such as exercise programs, nutritional support, and psychosocial support [7]. The literature on prehabilitation is rapidly evolving and has highlighted prehabilitation as a useful clinical tool that might attenuate the anticipated preoperative health deficits associated with a cancer diagnosis and its treatments [8]. For instance, patients with cancer are more prone to be in a catabolic state due to neoadjuvant therapies, which adds to the symptom-related burden of the disease and alters dietary patterns [9]. Management of such comorbidities by prehabilitation has been demonstrated to have potential for improving patient fitness, patient-reported health outcomes, and perioperative outcomes [10-12]. These interventions may be especially applicable in the context of the pandemic in view of the extended waiting times to access surgery [3,4,13].

Teleprehabilitation was defined in a previously published commentary by our group in 2020 [5] as the use of technologies to deliver health interventions to patients prior to surgery. Briefly, the commentary elaborated on the benefits and opportunities of using various technological tools available [14,15]. The commentary suggested that combined systems of videoconferencing and wearable devices may be optimal in providing personalized feedback [5]. Videoconferencing has been proven to be feasible and beneficial [16] for delivering rehabilitation, nutritional counseling, and psychological counseling [17-20]. Furthermore, wearable devices, such as training watches, can provide quantifiable feedback to users, which raises awareness of their daily habits (eg, sleep [21], physical activity [22], or inactivity [23]) in order to improve their lifestyle; this is especially important for this high-risk population. However, there is little to no literature on the subject for elderly populations in an acute context, such as the preoperative period [24], and for multimodal teleprehabilitation interventions.

This proposal has been set up to investigate the use of technologies, such as videoconferencing and training watches [5], to enable our prehabilitation clinic to continue to support people with cancer in a virtual format and deliver safe remote counseling by specialist health care providers. The goal of this study is to demonstrate the feasibility and safety of multimodal prehabilitation administered via videoconference. These outcomes have been targeted due to a lack of process and system outcomes being reported in the literature, specifically regarding multimodal interventions and combined technology systems, which, to our knowledge, are almost absent from the literature [15,24]. We hypothesized that it will be feasible to recruit patients with cancer requiring surgery and administer a 4-week individualized prehabilitation program that is delivered virtually. Further, we hypothesize that less than 5% of patients will experience severe adverse events related to teleprehabilitation interventions.

Methods

Ethics Approval

The trial protocol was approved by the Research Ethics Board (REB) of the McGill University Health Centre (MUHC), Montreal, Quebec, on January 5, 2021 (trial identification No. 2021-6730; protocol amendment No. V-04). The trial was registered prospectively on March 16, 2021, on ClinicalTrials.gov (NCT04799561).

Study Design

The protocol is for a single-arm feasibility study. It involves patients who will receive distance-delivered support for all components of the home-based prehabilitation program following a baseline health evaluation, in addition to 2 months of follow-up postsurgery. The program includes a personalized exercise program, nutrition support, mental well-being consultations, and, if needed, smoking cessation support. The technologies (ie, a tablet and an activity-monitoring watch) will be used to provide personalized counseling and patient education remotely and to assess program adherence. Informed consent will be obtained from all patients, as per the Health Canada regulations enforced by the REB, and will precede any assessments.

Inclusion and Exclusion Criteria

Patients will be deemed eligible for the study if they are 18 years of age or older, have been referred for elective surgical management of thoracoabdominal cancer at one of the MUHC sites, and have been medically cleared for exercise by their surgeons. The research staff will not contact patients who are anticipated to receive surgical interventions in less than 4 weeks from the referral date.

Prior to recruitment, the medical research team will screen all patients for health conditions that might preclude their participation in the prehabilitation program by reviewing their medical files and, if necessary, contacting them over the phone.

Exclusion criteria for participation in the study are as follows: comorbid medical, physical, or psychological conditions, whereby exercise and oral nutrition is contraindicated; acute or unstable cardiac conditions; American Society of Anesthesiologists physical status class of IV or V; disabling orthopedic or neuromuscular disease; psychosis; dementia; cardiac failure (New York Heart Association functional class

of III or IV); severe chronic obstructive pulmonary disease (forced expiratory volume in first second of expiration <50% predicted); end-stage liver or kidney disease; and severe anemia (symptomatic or hematocrit <30%). Patients with poor comprehension of the English or French language will not be recruited.

Patient Recruitment

The recruitment process will begin at the MUHC following cancer diagnosis by surgical investigators. Surgeons will refer prospective study candidates to the study coordinator in the prehabilitation unit, who will then screen and contact patients and explain to them the nature of the study. If the patients express interest, they will be scheduled for an initial visit at the prehabilitation unit to review the study, provide consent, and undergo a baseline health evaluation. During the initial visit, the coordinator will review the details of the study with the patient, provide clarifications as needed, and acquire informed consent in accordance with good clinical practice guidelines. It will be reiterated that participation in the trial is voluntary, and involvement will not affect the quality of care that patients receive. Following the acquisition of informed consent, the baseline evaluation will be conducted by a physician, exercise physiologist, and dietician.

Baseline and Follow-up Assessments

Prior to performing the baseline assessment, basic health information will be obtained, including the following: (1) prior medical history, (2) standardized anthropometric measurements (ie, height, weight, and waist and hip circumferences), (3) a bioelectric impedance analysis, and (4) a basic blood test (ie, hemoglobin, albumin, prealbumin, creatinine, C-reactive protein, and B-natriuretic peptide). The baseline assessment will include functional tests, a nutritional consultation, and self-reported questionnaires.

The clinic will have all patients perform a battery of tests, which will be used to assess functional capacity, facilitate the personalization of their respective exercise prescriptions, and help in evaluating progress throughout the continuum of care. The battery of tests will include the following: (1) the 6-minute walk test performed in accordance with the recommendations of the American Thoracic Society [25], (2) the timed up and go test [26], (3) the timed sit-to-stand test [27], (4) handgrip strength measured using a hand dynamometer [28], and (5) a timed unilateral curl test [29].

All patients will receive a nutritional consultation with a registered dietician to review dietary habits, assess their nutritional status and risk of malnutrition, and determine their optimal nutritional intervention. The dietician will consult several measures, such as anthropometric data, a complete 3-day food log, recent blood tests (ie, albumin, C-reactive protein, and hemoglobin A_{1C}), and an MUHC abridged Patient-Generated Subjective Global Assessment (aPG-SGA) [30], in addition to functional measures (ie, handgrip strength).

Patient-reported measures are important and are often overlooked in the clinical setting. Therefore, patients will be asked to complete questionnaires that subjectively assess the following: functional capacity (ie, the Duke Activity Status Index [31]), quality of life (ie, the EQ-5D [32]), mental well-being (ie, the Hospital Anxiety and Depression Scale [33]), psychological distress (ie, distress thermometer), physical disability (ie, the World Health Organization Disability Assessment Schedule, version 2.0), and energy expenditure (ie, the Community Healthy Activities Model Program for Seniors [34,35]).

Following the baseline assessment, patients will be provided with a Samsung tablet and Polar training watch; they will also be given access to a 45-minute technical workshop on the different preset apps, utilities, and educational video content available [36]. Patients will receive the multimodal prehabilitation services until their respective surgeries; the prehabilitation services will include a personalized exercise program, nutritional guidance and supplementation, psychosocial counseling, and medical optimization as deemed necessary. The exercise physiologists will monitor and interact with patients remotely with weekly virtual counseling sessions, and they will liaise with the multidisciplinary team to provide updates on patient progress. Therefore, patients will only have to come to the hospital for essential medical appointments. Patients will have assessments performed at four time points: at baseline, 24 hours prior to surgery, 4 weeks after surgery, and 8 weeks after surgery.

Interventions

Overview

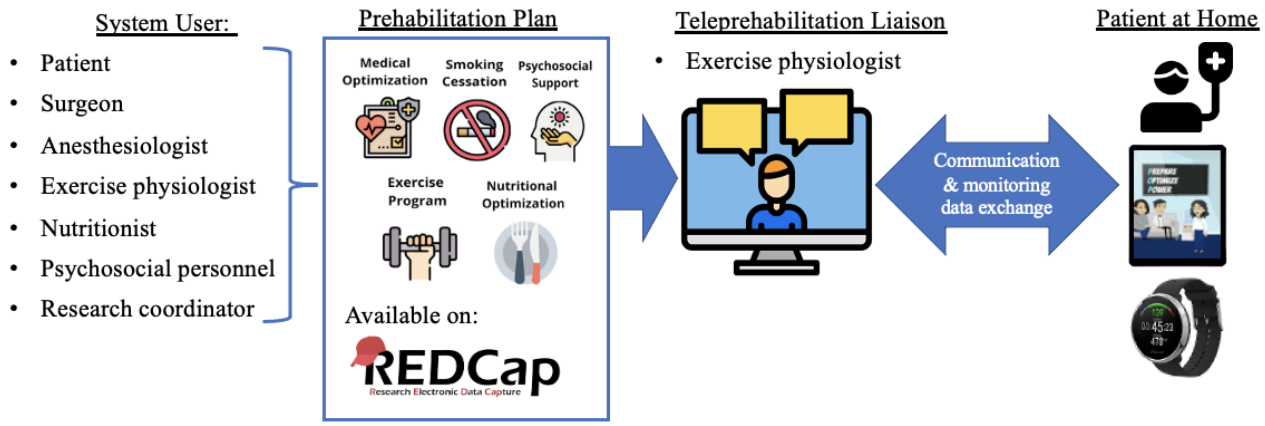
The program to be provided to patients is two-fold: the first part consists of individual counseling sessions with different health care professionals, and the second component is a home-based prehabilitation program, whereby patients will be remotely followed by exercise physiologists.

The multidisciplinary prehabilitation team will be available to further support patients and their respective needs (ie, exercise, nutrition, and psychosocial support). If needed, health care professionals will be able to contact patients via the Zoom videoconferencing platform (Zoom Video Communications, Inc) [37], which will be facilitated using the tablet provided.

Exercise physiologists will follow up with patients regularly throughout the continuum of care (ie, before and after their surgery) [38] and refer them to the relevant specialists as needed; see Figure 1 for the patient-centered delivery-of-care plan.

On their tablets, patients will have access to premade educational videos to provide them with further support and guidance on the following important health concepts: physical activity (ie, aerobic, resistance, and flexibility), nutrition optimization (ie, healthy eating, improving protein and energy intake, portion size, and glycemic control), psychological exercises (ie, breathing exercises, relaxation, imaging, and visualization), and smoking cessation.

Figure 1. Patient-centered delivery-of-care model.



Recommended Exercise Program

As previously discussed, patients' mobility and capacity to undertake exercise will be evaluated before creating the personalized exercise program. They will be provided with explanations about the program, and their adherence to the program will be monitored and facilitated by the Polar watch provided. Patients will be instructed on how to perform aerobic exercise at home by either walking or cycling (ie, beginning at 50% of their respective heart rate reserve for a minimum target of 30 minutes per day, minimum bouts of 10 minutes, five times per week). The exercise physiologists will adjust the exercise volume or intensity in a stepwise fashion, increasing it by 10% per week, if tolerable. Resistance training will also be encouraged, and patients will be asked to complete a series of eight exercises targeting the major muscle groups three times per week. The exercises will be performed using body weight, elastic bands, or both; two to three sets of 8 to 12 repetitions will be performed.

Physical safety will be addressed before establishing the recommended exercises by evaluating the patient's functional capacities, prior injuries, and physical limitations. This ensures the safety of every patient in the physical activity program that will be done at home.

Nutritional Component: Supplementation and Follow-up

The patient's nutritional status and dietary intake will be assessed by the nutritionist. The dietician will consult basic anthropometric and laboratory measures, in addition to a nutritional screening tool (ie, the aPG-SGA [30]), in order to help them assess each patient's dietary needs and extent of nutritional disparity, if present. All patients will receive daily dietary supplements of whey protein. Special precautions will be taken if patients have specific medical conditions (eg, diabetes).

The nutritionist will assess and counsel patients through the videoconferencing app within the first week of enrollment. If needed, additional counseling sessions will be possible through the same platform, depending on patients' needs. Adherence to the nutritional recommendations will be assessed by having the patient take pictures of their meals one day per week, which will be sent to the dietician.

Psychological Component

Patients will be allocated up to 1.5 hours of counseling with a psychology-trained specialist through the teleconferencing app so they can learn mental relaxation and coping mechanisms. Given that patients may experience varying degrees of emotional distress, more sessions can be provided if needed.

Lifestyle Modification Component

Patients with smoking habits will meet with a respiratory specialist through videoconferencing. The respiratory specialist will establish recommendations and contact the physician for the recommended smoking cessation protocol. The respiratory specialist will explain the use of an inspiratory muscle training (IMT) device to be used at home. The patient will be instructed to use the IMT device every day for a minimum of two series of 30 breaths each. Weekly improvements will be assessed through home-based videoconferencing.

Material for Patients

In addition to the standard material provided in previous prehabilitation studies (ie, booklet, nutritional supplement, relaxation recording, elastic band, and IMT device), patients in this cohort will have access to two technological tools. These tools will be used to create the telehealth system that allows for interaction between the prehabilitation team and patients during different parts of the program. The two tools, as seen in Figure 2, are (1) a Polar watch and (2) a Samsung tablet, which is loaned to patients for the duration of the study with its respective charger.

The first tool is a Polar Ignite fitness watch. This watch will allow patients to monitor their heart rate and physical activity volume during aerobic and resistance training, in addition to daily activities, directly on their watch or on the app installed on their tablet. For patients to view their physical activity data on their tablet, they must synchronize their watches with the Polar app on their tablet using Bluetooth. It is recommended that they synchronize their watches daily. The information collected from the watch will be uploaded instantaneously onto their Polar personal account when the tablet is connected to the internet. Since patients' "personal" Polar accounts will be connected to the exercise physiologists' "coach" accounts (ie, accounts for exercise physiologists to access their patients'

activity logs) prior to provision of the technologies, the daily physical activity information uploaded by the patient will be able to be remotely viewed instantaneously by the prehabilitation team. The information collected (ie, minutes of physical activity, heart rate, and daily step count) will help the prehabilitation team set weekly goals with the patients and monitor their progress.

The second tool is a Samsung tablet. The tablet will create a platform of communication between the patient and the multidisciplinary prehabilitation team. On the tablet, which will be provided with data (ie, internet access), patients will have access to the following: (1) reference videos about the different aspects of their prehabilitation program, (2) a videoconferencing and chat app to communicate with their family and health care professionals (ie, Zoom), (3) a calendar to remind them of counseling appointments, (4) a daily three-question survey concerning adherence, (5) an app to track their physical activity progress, (6) audio recordings for relaxation and coping exercises, and (7) questionnaires and tools for the baseline assessment, preoperative assessment, and postoperative follow-ups. The MUHC information technology (IT) department will format the tablets with their content and apps. This will ensure that all materials will have the same settings with the right security settings applied.

Figure 2. The technological tools of the telehealth system.

Outcomes of Interest

The primary outcome is feasibility of teleprehabilitation for high-priority patients with cancer. The criteria to evaluate feasibility are as follows: (1) the recruitment rate, (2) remote access and collection of outcomes measured via technology tools in 70% or more of the patients weekly (eg, step counts and heart rate), (3) an average attendance rate for all components of the multimodal prehabilitation program of 71% or higher (ie, attendance at monitored virtual sessions and independent home-based exercise sessions), and (4) a retention rate of 66% or higher. The rates of recruitment, adherence, and retention will be compared to target thresholds. The recruitment rate is defined as the proportion of eligible patients that consented to participate in the study and is considered to be adequate if greater than 80%. Program adherence is a multifaceted parameter; in this study, adherence will be based on attendance at the synchronous teleprehabilitation sessions and completion of home-based aerobic and resistance exercise sessions that were prescribed. Therefore, adherence to the exercise or teleprehabilitation sessions will be based on the number of sessions completed relative to the number that were prescribed. In a hypothetical example, a patient could be prescribed one teleprehabilitation session, three aerobic sessions, and two resistance sessions per week for a 4-week duration, and they could complete three, 10, and five sessions, respectively. Therefore, their adherence to each component would be 75%, 83%, and 62%, respectively. The total adherence is based on an equally weighted distribution across the above-mentioned components (ie, teleprehabilitation, aerobic, and resistance sessions); therefore, the final attendance score would be 73%. The target threshold for adherence is 71%, which was derived from internal historical data [39]. Retention refers to the number of patients that complete the program with reference to those that consented and is considered to be a success if greater than 66%. Additionally, qualitative measures, such as rationale for refusal to participate, low adherence, and number of dropouts, will be collected to provide more contextual information for interpretation.

The secondary outcome is the safety of delivering telerehabilitation interventions. It will be documented by the occurrence of program-related adverse events, as elaborated by the typology by Ory et al [40] for exercise. The study will be considered safe if the incidence of serious adverse events represents 5% of patients or less. Serious adverse events will be considered as events that would prompt the interruption of the exercise session or the program [41]. The exercise physiologists will question patients on the occurrence of adverse events during weekly synchronous teleprehabilitation sessions. Events will be reported in a timely manner to the physician coinvestigators at the prehabilitation clinic, who will evaluate the severity of the event and the need for temporary or permanent discontinuation of the program, if necessary. Patients will continue to be followed by our research team until the end of the study, even if the exercise program is interrupted (ie, 8 weeks after surgery).

Statistical Considerations

Descriptive analyses, including means and proportions, will be used to compare demographics and the baseline functional and pathological states of those who remain in the study until completion, as well as those who drop out. This is an essential step to establish that the sample is representative of the population and to mediate potential demographic status biases. Means and SDs will be reported when data are normally distributed, as parametric analyses will be selected. A nonresponse analysis will be conducted using chi-square tests and two-sample *t* tests.

To assess feasibility, the recruitment, completion, and adherence rates will be computed. A one-sample 2-sided *z* test will be performed on the respective rates, with thresholds set at 80% for recruitment and completion and 71% for adherence, based on internal historical data. To assess the adherence rate of individual patients, the completion status of synchronous teleprehabilitation sessions and home-based exercise sessions will be evaluated in a dichotomous manner and will be subject to a proportion of completed sessions that were prescribed. The weekly proportion of completed prescribed sessions will be summed over the whole duration of participation (ie, 4 weeks), and an individual adherence score will be calculated, with equal weights for teleprehabilitation sessions, aerobic sessions, and resistance sessions. Lastly, the individual attendance scores will be pooled with others for the *z* test analysis.

To assess safety, descriptive statistics will be used to report adverse events by type of event (eg, musculoskeletal and cardiac) to establish incidence. The threshold to conclude that teleprehabilitation is safe is a 5% or lower incidence of severe adverse events.

These calculations will be performed using SPSS Statistics for Windows (version 24.0; IBM Corp), with the CI and significance levels preset at 95% and .05, respectively.

Sample Size and Timeline

The sample size will be based on the evaluation of adherence to the home-based prehabilitation program. In a previous home-based study, we reported an adherence rate to prehabilitation of 78% (n=38) [38] prior to surgery. We assume that the adherence rate in this study will not be much lower because, despite being isolated at home, patients will have access to videos and a watch, which will encourage them to be active and engaged in the program. As per our experience, we expect 20% refusal to participate and 20% loss to follow-up. Approximately 500 patients each year undergo operations at the Montreal General Hospital (MGH) for lung, esophageal, stomach, and colorectal cancer.

Confidentiality

The technologies in this project (eg, the Zoom videoconferencing platform and the Polar watch app) use confidential information (ie, emails and names). Patients will receive the materials (ie, tablet and watch) with preset accounts from the MUHC IT department, fully coding their identity, where both their names and emails will be coded. Patients will be encouraged to read the privacy notices for both the Polar and Zoom apps. Further, the Polar Ignite watch has a GPS that will record location and distances traveled when activated during cardiopulmonary training sessions. This information will be disclosed to patients, as it may play a role in patients' willingness to participate.

Data Collection, Storage, Security, and Handling and Record Keeping

The research coordinator (BT) and the principal investigator (FC) will assign identifiers to each study participant. These ID numbers (ie, PPP1 to PPP100) will not contain any protected health information (eg, social security number and medical record number).

The information collected for the purpose of the research study will be kept strictly confidential and locked in a cupboard within a locked room in the prehabilitation clinic at MGH. All staff, including students, have signed a confidentiality agreement. The password-protected computer where data will be entered is located in a locked room and is not accessible to patients or external members of the hospital.

Since the tablets will be provided with internet data and connection, the cookies will be disabled by the MUHC IT department. Additionally, patients will be asked to close their internet browser after each counseling appointment in order to maximize privacy and data protection.

All information (ie, demographic data, clinical data, patient-reported questionnaires, and adherence data) will be entered and managed in REDCap (Research Electronic Data Capture), a secure clinical trials management system. Data will be stripped of any identifying information (eg, name and address), and each subject will be assigned a study number. All of the information obtained will be treated in a confidential manner.

Study investigators, approved staff, collaborators, and the local REB will have access to review records for research, quality assurance, and data analysis. Data collected before the moment when patients express their wish to stop participating or when patients are lost to follow-up will be able to be analyzed in a confidential manner unless otherwise specified by the patients.

Following the closure of the study, the principal investigator will maintain all study records in a safe and secure location for 7 years, as specified by local regulations. The records will be accessible to allow for appropriate audits and investigations.

Results

The MGH Foundation funded the project in August 2020. The study recruitment period started on March 12, 2021, with the first patient also recruited in March 2021. As of March 2022, 36 patients have been recruited, including 24 patients who have completed their participation, 6 of whom were unable to complete their 4- and 8-week postoperative evaluations. Currently, there are 12 active participants who are still a part of the teleprehabilitation pathway. None of the participants reported any program-related adverse events. Recruitment is expected to conclude in September 2022, and data collection is expected to conclude in November 2022. Data analysis will be performed, and the results will be published by the beginning of 2023. Following the completion of the study, the results will be communicated in a peer-reviewed journal.

Discussion

This study is a single-arm clinical trial that aims to investigate the safety and feasibility of delivering teleprehabilitation to patients with cancer who will undergo surgery. There are currently 36 patients recruited, 24 of whom have completed their participation. This is one of the first studies to use technology-assisted interventions in the preoperative setting. Due to the nature of the research, this study may face several challenges and limitations pertaining to (1) the study design, (2) public health measures and disease management, (3) and technologies.

The study design used is inherently subject to various biases due to the lack of a control group or randomization. First, selection bias may be of concern because the study may involve individuals who are more able to participate in the program, especially regarding the exercise component, or who are motivated and, hence, they may be part of a more compliant population. To mitigate the risk of selection bias, we offered participation in the study to all eligible patients who were referred to the clinic, providing technologies for all patients, including those with precarious socioeconomic status. Additionally, to mitigate the risk of misrepresentation of the population, baseline characteristics of patients will be analyzed in order to determine if the observed demographic and exercise capacities are comparable to other trials with surgical oncological candidates. Second, patients involved in the trial may have distinct levels of adherence to the different interventions. To prevent misrepresentation, adherence will be assessed separately for the different components of the program.

The COVID-19 pandemic has impacted the lives of millions of people around the world. COVID-19 pandemic restrictions are still being implemented and will likely remain for the foreseeable future. Upon the new waves due to emerging variants, two potential limits can be foreseen. First, it is possible that patients with cancer may be reluctant to come to the clinic for assessments. To mitigate this challenge, the multidisciplinary prehabilitation team will try to time in-person assessments to coincide with the patients' other medical appointments. Second, the surgical backlog associated with the first waves of COVID-19 have led to patients missing their window for curative tumor resection of early-grade malignancies [2]. This may present a challenge in prehabilitation, as many patients may experience modifications in their disease management strategies, which can contribute to an elevated dropout rate. To mitigate the misinterpretation of the dropout rate, patients who drop out of the teleprehabilitation program will be asked their motive for doing so.

The technologies in the study constitute another challenge that may limit both data collection and interpretation. There are three technology-related limitations that can be foreseen for data collection. First, patients may not wear the wearable device (ie, sport watch) for the same number of days or hours within a day. Second, the battery in the device could run out. Third, patients could forget to record their training sessions [42]. All of these could impact the validity of the daily measurements and prompt difficulties when pooling the data from different patients together. This challenge of validity can be mediated in two ways. First, the exercise physiologists could be provided with common training on the technologies and the anticipated technical challenges in order to be able to readily provide support to patients. Second, continuous patient feedback could be provided during synchronous teleprehabilitation sessions relating to patients' real activities if they experienced technological challenges. For example, if a patient has forgotten to stop a training record on their watch, the record may show a 5-hour exercise session, but through the active investigation and open communication between the patient and the exercise physiologist, correction of the erroneous data could be highlighted. Moreover, an additional limitation could be that interpretation of the data can be overwhelming due to the large amount of data collected from each patient daily (ie, multiple time points across the program). This prompts the need for careful statistical considerations when evaluating adherence. To mitigate this challenge, the prehabilitation team will consult a statistician in the conduct of the statistical analyses.

In conclusion, this trial will provide important insights into the use of telehealth in the administration of prehabilitation services. The trial will provide a large amount of information that will respond to gaps in the literature, as there are minimal reports on the use of telehealth rehabilitation and prehabilitation services among elderly populations and in acute contexts, such as the preoperative period [24]. Further, in the context of the evolving pandemic, it can be foreseen that such intervention methodologies will become important tools in providing supportive care to patients with cancer at different institutions in the near and distant future [2].

Acknowledgments

This research project received funding from the MGH Foundation to buy the technologies and from the Peri Operative Program Foundation to pay the staff working at the prehabilitation clinic.

Data Availability

The principal investigator (FC) and the research coordinator (BT) will have full access to the final database; data will be available upon reasonable request. The results of the study will be presented in a peer-reviewed journal and international conferences and will be clearly reported on ClinicalTrials.gov.

Authors' Contributions

All authors contributed significantly to either the elaboration or writing and review of the trial, with GL and FC as the main contributors as first author and principal investigator, respectively. KD assisted in the revision of the paper, and BT assisted with the coordination of the system and study. All authors read and approved the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

aPG-SGA: abridged Patient-Generated Subjective Global Assessment
IMT: inspiratory muscle training
IT: information technology
MGH: Montreal General Hospital
MUHC: McGill University Health Centre
REB: Research Ethics Board

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Protocol

Ethical, Legal, and Social Implications of Symptom Checker Apps in Primary Health Care (CHECK.APP): Protocol for an Interdisciplinary Mixed Methods Study

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Abstract

Background: Symptom checker apps (SCAs) are accessible tools that provide early symptom assessment for users. The ethical, legal, and social implications of SCAs and their impact on the patient-physician relationship, the health care providers, and the health care system have sparsely been examined. This study protocol describes an approach to investigate the possible impacts and implications of SCAs on different levels of health care provision. It considers the perspectives of the users, nonusers, general practitioners (GPs), and health care experts.

Objective: We aim to assess a comprehensive overview of the use of SCAs and address problematic issues, if any. The primary outcomes of this study are empirically informed multi-perspective recommendations for different stakeholders on the ethical, legal, and social implications of SCAs.

Methods: Quantitative and qualitative methods will be used in several overlapping and interconnected study phases. In study phase 1, a comprehensive literature review will be conducted to assess the ethical, legal, social, and systemic impacts of SCAs. Study phase 2 comprises a survey that will be analyzed with a logistic regression. It aims to assess the user degree of SCAs in Germany as well as the predictors for SCA usage. Study phase 3 will investigate self-observational diaries and user interviews, which will be analyzed as integrated cases to assess user perspectives, usage pattern, and arising problems. Study phase 4 will comprise GP interviews to assess their experiences, perspectives, self-image, and concepts and will be analyzed with the basic procedure by Kruse. Moreover, interviews with health care experts will be conducted in study phase 3 and will be analyzed by using the reflexive thematical analysis approach of Braun and Clark.

Results: Study phase 1 will be completed in November 2021. We expect the results of study phase 2 in December 2021 and February 2022. In study phase 3, interviews are currently being conducted. The final study endpoint will be in February 2023.

Conclusions: The possible ethical, legal, social, and systemic impacts of a widespread use of SCAs that affect stakeholders and stakeholder groups on different levels of health care will be identified. The proposed methodological approach provides a multifaceted and diverse empirical basis for a broad discussion on these implications.

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KEYWORDS

symptom checker apps; self-diagnosis, self-triage, digitalization in primary care, general practitioners; symptom checker; app; mobile app; primary care

Introduction

Background

The number of health-related software in consumer and research-oriented apps is increasing rapidly. Symptom Checker Apps (SCAs) are one example for health-related software that could have a major impact on health systems on all levels. SCAs process medical symptoms that users enter by applying algorithms and databases with medical information [1]. Based on these symptoms, SCAs generate a list of probable causes and suggest medical follow-up actions (eg, wait at home, see a doctor, go to the emergency room). The Google Play Store already lists 249 apps (retrieved on March 24, 2021) for the key words "symptom checker" [2]. Some SCA manufacturers advertise that they have implemented artificial intelligence [1,3,4] and big data as the basis of their apps. For example, as described by Richens et al [5], the SCA "Babylon" uses a causal machine learning approach based on a Bayesian approach combined with counterfactual inference. The presented algorithm achieved expert clinical accuracy for a test set of clinical vignettes [1]. It, however, remains unclear how well it performs in real-life situations. Although there have already been strong claims from ethical research that emphasize the significance of criteria such as transparency, trustworthiness, agency, and responsibility for artificial intelligence–driven decision support systems such as SCAs [6-8], not all manufacturers using artificial intelligence consider these criteria, and it is mainly untransparent how user data are processed and algorithms are trained.

The regulation of SCAs varies in different countries. In some countries, SCAs are effectively unregulated (eg, Australia [9]); in others, SCAs are regulated but with a period of "enforcement discretion" without active regulatory (eg, US Food and Drug Administration [10]). In the European Union, there is a transition between regulation through manufacturer "Declaration" of conformity to legislation toward a model of regulator audit of compliance with standards, including the formal reporting and evaluation of specified forms of clinical data and surveillance trends [11].

Symptom checkers are low-threshold tools that can be accessed with a suitable electronic device with internet access such as a smartphone and are available as apps or as browser versions. Users must be able to interact with technical devices and to interpret the SCA's output to utilize them properly. This could lead to a disadvantage of specific population groups, for example, older adults, people with disabilities [12], or people with limited economic resources [13]. Some SCAs exclude specific user groups for symptom analysis, for example, pregnant women, children, older adults, and patients with specific comorbidities [14].

A recent study by Aboueid et al [15] investigated the intention to use symptom checkers for self-triage and revealed 5 profiles by using a latent class analysis: tech acceptors, tech rejectors, skeptics, unsure acceptors, and tech seekers. Tech seekers, which were described as participants who have positive perspectives related to SCA functionality and artificial intelligence but do not perceive to have access to the technology, showed the highest odds to use SCAs. However, the sample investigated only students aged between 18 and 34 years [15].

Although some users found that SCAs are useful tools for self-diagnosis and even reported positive health effects [16], other users had problems providing and interpreting concrete information on symptom time patterns or severity [17].

SCAs recommend actions and probable causes for the entered symptoms through their output if the output is incongruent with the users' experience or if expectation discrepancies arise [18] and may initiate unnecessary health care–seeking behavior [19].

In terms of their medical value and validity, commercially available SCAs still have problems with accurate triage (determining a user's medical condition based on their input and recommending the optimal health-related actions for the user). Several studies showed that SCAs often suggested risk-averse action recommendations [20-22]. SCA diagnostic and triage accuracy is still limited and was even less reliable in nonurgent scenarios, which are common in primary care [20,23]. A recently published study compared the performance of SCAs (n=8) with the performance of telephone consultation with the general practitioner (GP) (n=7) by using case vignettes (n=100). GPs outperformed SCAs on all assessed outcomes (accuracy, condition suggestion, appropriateness, and safety of urgency advice). The comparison was limited to telephone consultations and did not comprise direct patient-physician contact. Another recent study compared the performance of SCAs to that of medical laypersons using clinical vignettes and found that most laypersons outperformed the majority of SCAs, even though SCAs detected emergency cases more reliably than the laypersons [23].

In high-performing health care systems, inaccurate triage can cause preventable costs and increase the risk of unnecessary procedures that could lead to avoidable risks for patient's safety [3,24]. However, in structurally weak regions with restricted access to medical care, SCAs can provide a first-line assessment that otherwise would not be available [25].

In summary, the potential risks of the use of SCAs (exclusion of users, stress, and induction of health-seeking behavior) contrast the advertised opportunities of SCAs such as patient empowerment and better health care for underserved regions. There is a substantial gap in the literature concerning the effect of SCAs on different health care systems, different levels of health care (microlevel, mesolevel, and macrolevel [26]) within these systems, and the system's different participants (users,

nonusers, and health care providers). If SCAs become more widely used, their ethical, legal, social, and systemic impacts on these levels and participants must be better understood despite complex interactions and methodological challenges. In this study, we aim to clarify the ethical, legal, social, and systemic impacts of SCAs on users, nonusers, GPs, the primary health care systems, and their work by means of an independent, empirical, integrated multi-perspective, and multidisciplinary discussion.

Objectives

Owing to the lack of systematic research of SCAs in primary health care, the recent study uses an explorative hypothesis-generating approach in which the abovementioned discussion is informed by 4 foci of interest and the study aims, as stated in the following section.

Focus 1: Ethical, Legal, and Social Issues of SCA Use

We aim to identify the ethical, social, and legal subjects in the recent scientific literature on SCAs (eg, usage linked to inequities in health care, patient autonomy, modification of role concepts and agency).

Focus 2: SCA Epidemiology, Users, Nonusers, and Predictors of Use

Our results will contribute to describing the user group and nonuser group of SCAs in more detail. The degree of use of SCAs in Germany will be derived, and predictors for SCA use will be identified. Moreover, vulnerable groups that might be disadvantaged through the implementation of SCAs will be described.

Focus 3: Patterns and Impact of SCA Use and the User Level

As a goal for the users' perspective, a comprehensive description of SCA use will be derived. This will comprise the assessment of requirements that are fulfilled or unfulfilled by SCA use. Additionally, we aim to identify the possible risks associated with SCA use and assess how users handle SCA information and action recommendations. SCA effects on user agency, health and eHealth literacy, well-being, and self-care will also be observed.

Focus 4: Impact of SCA Use on Health Care Systems and Health Care Workers

We will specially focus on considering the impact of SCAs from a health system perspective by assessing the following: changes in the patient-physician relationship, strategies of handling preinformed patients, changes in the role concept of physicians and requirements of GP, as well as potential psychosocial risks and demands and perceived work stress resulting from these changes.

Methods

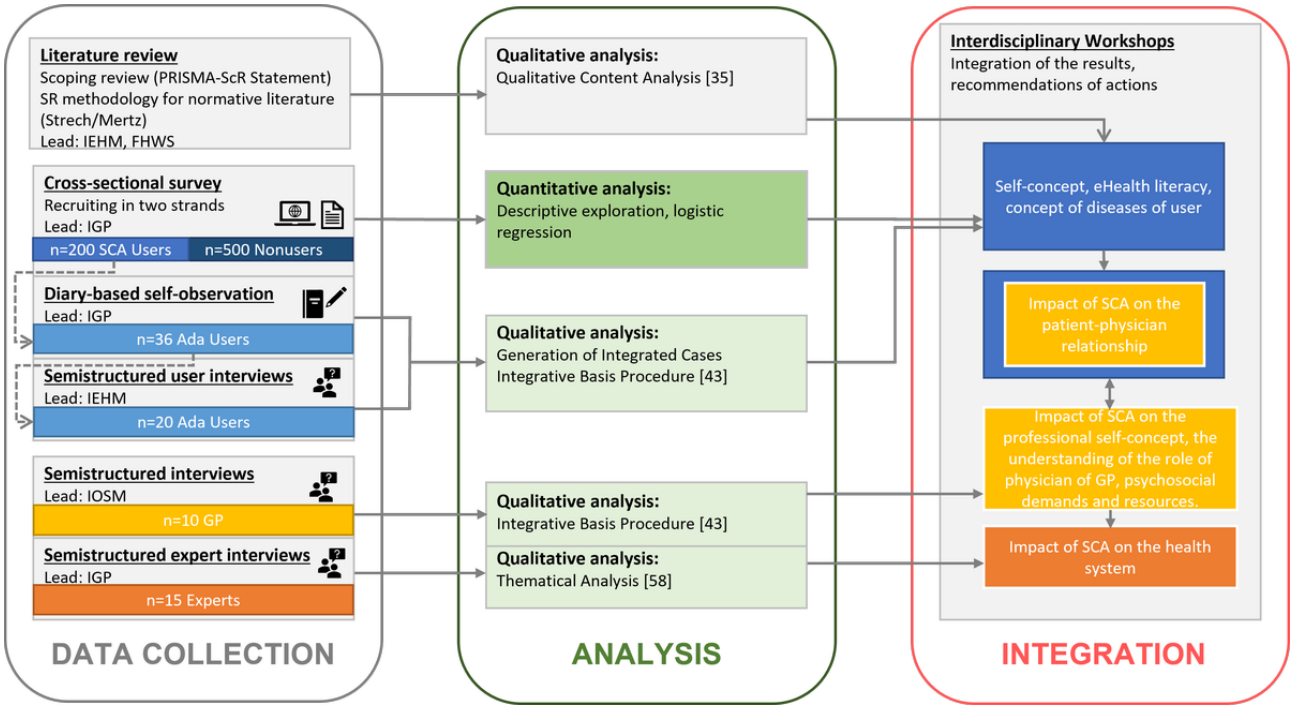
Study Design

This study's areas of focus and corresponding study phases will be conducted by multidisciplinary partners from the areas of social medicine, ethics and medical history, legal studies, general practice, sociology, occupational health medicine, and health services research. We will investigate SCAs that offer self-triage and action recommendations for medical laypersons. The project partners will co-develop study materials, subsequently discuss results, and conduct method workshops throughout the 3 years. During the final study year, a series of workshops will include participants of the preceding study parts. This workshop series during the final year is led by a social scientist with comprehensive experience of working in cross-disciplinary research and holding method workshops. The workshops will also serve as internal quality control and monitoring. An advisory board is continually informed about the progress and the results of the study phases. Members of the advisory board will be recruited from different contexts and disciplines. The advisory board will meet annually to give feedback on the research process, preliminary results, and the dissemination of the latter.

Ethical Considerations

The German Federal Ministry of Education and Research funds the project for 3 years (Grant 01GP1907A). Ethical approval for this study was obtained from the ethics committee of the University of Tübingen (ID: 464/2020BO). This study will be conducted in accordance with the Declaration of Helsinki. Study participants will be informed thoroughly about the study and their rights, and written informed consent will be obtained from all study participants. Other research ethics requirements such as data protection will be diligently considered. The general study design and the involved research partners are outlined in Figure 1.

Figure 1. Overview of the study design, research partners and analysis methods. IEHM: Institute of Ethics and History of Medicine, University Tübingen, IGP: Institute of General Practice and Interprofessional Care, University Hospital Tübingen, IOSM: Institute of Occupational and Social Medicine and Health Services Research, University Hospital Tübingen, FHWS: University of Applied Sciences Würzburg-Schweinfurt, SCA: Symptom Checker App.



Study Course

Four main data sources will be considered, each representing a specific stakeholder group of SCAs: representative sample of the German population (divided into SCA user and nonuser), GP, and health care experts. We define SCA users as participants that have used SCAs at least once, and nonusers are participants who never used SCAs. Data collection and analysis methods will comprise qualitative and quantitative approaches.

The different methods are applied to the data sources in 4 interconnected study phases, each representing one of the four main foci of interest of the study: a literature review (study phase 1, lead: Institute of Ethics and History of Medicine, University Tübingen [IEHM], Institute of Applied Social Science, University of Applied Science Würzburg-Schweinfurt), a representative survey of SCA user and SCA nonuser (study phase 2, lead: Institute of General Practice and Interprofessional Care, University Hospital Tübingen [IGP]), an SCA user diary-based self-observation combined with individual semistructured interviews (study phase 3, lead: IEHM), and lastly, single semistructured interviews with GPs and health care experts (study phase 4, lead: Institute of Occupational and Social Medicine and Health Services Research, University Hospital Tübingen [IOSM] for GP interviews, lead: IGP for health care experts interviews). For this study protocol, we will follow the Good Reporting of A Mixed Methods Study (GRAMMS) [27] checklist. Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [28,29], STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) [30], SRQR (Standards for Reporting Qualitative Research) [31], and GRAMMS [28] checklists will be applied during the project process. The PRISMA-ScR, STROBE, and SRQR guidelines will be applied on specific study phases. The GRAMMS [28] guideline will be used in the context of mixed methods approaches and in the integration of results. In the following sections, the 4 study phases and their connections are described in detail.

Study Phase 1: Literature Review

The first study phase will comprise a comprehensive literature review that will assess the existing research on SCAs and their impact on primary care. The aim of this study phase is to gain a clearer picture of the state of science of SCAs, considering the ethical, legal, social, and systemic (eg, risks, potentials) impacts of SCAs. A literature search, oriented on scoping review (ScR) methodology, will be conducted and reported according to the PRISMA-ScR statement [28,29]. In recent years, the ScR methodology has been adopted and further developed for the field of bioethics, which is characterized by normative research questions. When analyzing argumentative literature, adjustments need to be made to the “classic” ScR methodology [32-34]. Key terms will be defined for the search strategy regarding the research questions, and databases covering the relevant dimensions (biomedical, ethical, social, and legal) are selected (Web of Science, PubMed [Medline], Belit/Ethmed, ProQuest, SowiPort, GESIS, Philpapers, Juris, BeckOnline, etc). The inclusion criteria comprise either the mention of an ethical, legal, or social issue or a combination of this terms related to SCAs as a digital or mobile app, targeting medical laypersons that support the assessment of symptoms and self-triage or one of both aspects. Apps for health care professionals or other experts, as well as SCAs, which focus on a single health condition or certain groups of diseases were excluded. To present the full spectrum of ethical, legal, social, and systemic impacts literature relevant to the review question, not only

argument-based but also empirical literature was included. Publications on SCAs that were written in English or German and published until 2020 were included in the review. Journal articles, contributions to anthologies, reports, case series, letters to editors, opinions, commentaries, and conference papers were also included; web-based blogs have not been considered. Three researchers screened the identified literature via hand and database search and discarded publications not meeting the inclusion criteria. Publications were analyzed by 2 authors using the method of qualitative content analysis proposed by Kuckartz [35].

Study Phase 2: Cross-sectional Survey of SCA Users and SCA Nonusers

Structure

A survey will be used in a case-control design. The questionnaire was piloted with 5 participants and will take approximately 15-25 minutes for participants to complete. The survey will comprise different evaluated scales (for further details, see Multimedia Appendix 1) and sociodemographic variables as well as specific questions to the usage of SCAs. This study phase will be conducted and reported according to the STROBE statement [30]. Owing to the limited amount of literature on SCA users and nonusers, pilot interviews with 2 SCA users and 1 SCA expert will be conducted to ensure a meaningful concept selection for the survey. Simultaneously, concepts will be derived from existing literature that is connected to the use of health apps and could reveal the potential characteristics of the user group such as eHealth Literacy [36], personality [37,38], hypochondria [39], self-efficacy [40,41], and need for cognition [42]. Affinity for technology [43], satisfaction with the GP [44], and overall life satisfaction [45] will also be considered. Moreover, we will assess the perceived usefulness of SCAs and requirements for SCAs in open-ended questions of the survey since this might be a central aspect of acceptance of SCAs as the Technology Acceptance Model (TAM) induces. The TAM was already introduced by Davis [46] in 1989 and is based on the theory of reasonable action and the theory of planned behavior. The TAM (and its further expansions) is still one of the most prevailing models to examine factors affecting a users' acceptance of new technologies [47]. The model assumes a mediating function of perceived ease of use and usefulness in association with system characteristics and system usage [47].

Sample and Recruitment

The sampling process was conducted from November 2020 until the end of June 2021. A case-control design using 2 recruitment strands is planned. An a priori power analysis using PASS 2020 (v20.0.3, NCSS) revealed a sample size of 375 (β=.8, α=.05, nuisance parameter=0.2; n_{user}=188, $n_{nonuser}$=188) for an odds ratio of 2.5. The targeted odds ratio corresponds to a small-to-medium effect of Cohen *d* [48] and was selected because we consider that this will be an effect size that contributes a meaningful explanation of variance in the logistic regression. As this study has an explorative character, we could not derive theory-driven assumptions for a multivariate logistic regression. Hence, we based the power analysis on a univariate logistic regression. We will use a univariate logistic regression to identify meaningful predictors for the usage of SCAs and will moreover set up a multivariate model that includes all the identified predictors. Our multivariate model will be the first proposal and will need further research to confirm the univariate predictors in a multivariate model.

The sample will be composed of different recruiting strands to achieve a representative sample. In the first strand, German citizens will be contacted via mail to participate in the survey. The intended recipients will be representatively selected by an external partner (T + R Dialog Marketing and Acxiom). Further participants will be recruited via mailing lists of the University of Tübingen and the University Hospital of Tübingen, social media, and cooperating GP practices. After 3 months, the representativity of this sample will be checked. If the return rate is too low or if certain groups are not sufficiently represented, there will be additional recruiting via the proposed channels.

The second strand of the sampling process aims to integrate symptom checker users only. We expect only a small number of symptom checker users. To ensure a sample size of n_{user}=188, a targeted recruitment via social media advertisements and the social media channels of the University Hospital of Tübingen will be conducted.

Inclusion criteria in general are the ability to give consent and German language skills of at least B1 of the Common European Framework of References for Languages. Participants of the second recruitment strand can only be included if they have experience with SCAs.

Analysis

The level of use for SCAs, awareness of SCAs, and general interest in SCAs will be described using the first recruitment strand with descriptive statistics.

Following the case-control design, SCA users from the first and second recruiting strand will be matched with nonusers (matched controls) from the first recruitment strand. Significant predictors will be extracted with a logistic regression. A correction for multiple testing will be applied. The recent versions of SPSS (IBM) and R statistic (R Core Team) will be used for the analyses.

Study Phase 3: Diary-Based Self-observation Combined With Semistructured User Interviews

Structure

Study phase 3 investigates SCA users and their usage patterns and effects of SCAs on individuals. A specific SCA (Ada app) was chosen by the study team as an example since it is considered one of the most prevalent SCAs in Germany. Following web-based training, participants will engage in a diary-based self-observation. During the observation time of 6 weeks, participants will document their daily usage and nonusage of the Ada app. Next, individual semistructured user interviews are performed with the diary study participants. The interviews allow participants to reflect on values, concepts, and knowledge gaps. This allows a supplemental exploration of the experiences recorded in the diaries. The user interviews in this

study part will be conducted and reported according to SRQR statement [31].

Sample and Recruitment

For this study phase, 50 Ada users will be recruited from the SCA user strand of phase 2 and, if needed, additionally via social media. Considering a dropout rate of 30%, a sample size of 36 is assumed. Of these participants, 15 will be recruited for single semistructured interviews using maximum variation sampling. Sampling will consider the content of the diary-based self-observation, usage behavior of the app, medical indication, and socioeconomic factors. Sample size calculations of the interview phases are based on the 5D model of *information power* by Malterud et al [49].

All participants will receive web-based training on the self-observation period. The diary will be used to document symptoms and events, as well as other expected influencing factors such as stress or quality of life. Furthermore, it will offer structured questions about the use of SCAs and enable the participants to write down their own reports or short "field notes." Thus, participants will record and describe their experience, and how they dealt with action recommendations, appearing problems, emotions, etc. These notes will be used as a basis for the following semistructured interviews. The interviews will be conducted via video call, audio-recorded, and transcribed verbatim by a researcher from the IGP and the IEHM. The users will receive financial compensation both for the interviews and the participation in the member check meeting described below.

Analysis

The diary-based self-observation and the interview transcripts will be analyzed and integrated into cases. Triangulating the self-observation diary data with interview transcripts provides both prospective (longitudinal) and retrospective (narrative) insights. Quantitative results of the diaries (frequency of use, use of health care, symptoms, etc) will be considered as prospective observational outcomes and will be analyzed quantitatively. The user diaries give the opportunity to record detailed situational experiences—feelings and thoughts that probably cannot be remembered or recreated during an interview without them. However, the interviews will provide in-depth reports on values, concepts, gaps in knowledge, etc, that tend to remain invisible in the diaries. The qualitative analysis via Kruse's integrative basic procedure [43] will provide an overview of the recurring themes and patterns within each case as well as between cases. At the same time, it will allow a more holistic consideration of the data such as the analysis of semantics, grammatical structures, and metaphors to reveal latent meanings and the way users "make sense" of the app and derive meaning and understanding of the recorded events [50]. The qualitative analysis of the study is supported by MaxQDA [51]. A member check with participants of the interviews is planned, in which results of the cases are presented to study participants to enhance rigor.

The aim of the quantitative analysis is to identify meaningful predictors for the use of SCAs, taking the longitudinal data structure into account. A hierarchical model with 2 levels will be performed. Level two will comprise the daily measurements and will be nested in level one, which comprises the participants. The quantitative analysis of the diaries will be performed using a recent version of Microsoft Excel [52] and R Statistics (R Core Team).

Study Phase 4: Semistructured Interviews With GPs and Health Care Experts

Structure

The fourth study phase investigates the possible effects of SCAs on health care delivery, health care providers (module A), and the health care system (module B). As primary care is most affected by patients' usage of SCAs, we will interview GPs in module A. We will gain more insights into patients' usage of SCAs and similar application results in potential psychosocial demands, resources, and perceived work-related stress [53], especially regarding workload, work content, work organization, and social environment [54]. Module B aims to deliver a multi-perspective view on possible effects of SCAs on the health care system. To fulfill this aim, we will conduct interviews with health care experts with different backgrounds to assess the state of science of SCAs in practice from a multi-perspective standpoint. Moreover, we aim to identify which potential experts see for the future use of SCAs and to derive quality criteria for SCAs. This study phase will be conducted and reported according to SRQR statement [31].

Sample and Recruitment

In module A, the sample will consist of 10 GPs in Germany. We aim to build a heterogeneous sample regarding the GP (age, gender, and race) and their practices (structure and location of the practice, main patient clientele, and availability of web-based services). Sample size calculations of the interview phases in modules A and B are based on the 5D model of *information power* by Malterud et al [49]. An interview guide [55] will be developed, containing questions about preinformed patients and diagnosis in general, questions about SCAs, and similar apps with the example of the Ada app in particular. It will be developed by the IOSM and the help of feedback from the other project partners. The IOSM will apply various forms of sampling such as snowball sampling in the established networks of the IOSM and web-based research to ensure the stated heterogeneity of the sample. Two researchers of the IOSM will conduct the interviews mostly via video call due to the ongoing pandemic. The interviews are expected to last about 45 minutes and will be audio-recorded.

In module B, 10-15 experts on health care systems will be interviewed. Experts will be recruited consecutively and comprise politicians, information technology developers for medical software, patient advocates, representatives from jurisdiction, medical associations, and health insurances. We assume that 10-15 interviews will provide sufficient information power [49]. Each interview guide will be tailored to the respective expert. Possible topics are the implementation of SCAs, recent issues with SCA requirements, and how SCAs influence different players in health care. The interview guides will be developed by the team of the IGP with input from the other project partners. The experts will be contacted via already

existing research networks of the project partners. One researcher of the IGP will conduct the interviews mostly via video call. The interviews are planned to last about 45-90 minutes and will be audio recorded.

The expert interviews will provide an information background on the *status quo* of SCAs in health care as well as ideas for future developments. This background is important for the discussion of user experiences (Study phase 3) and for the patient-physician relationship (integrated study phases 3 and 4). All participants will receive financial compensation both for the interviews and the participation in the member check meeting.

Analysis

All interviews will be transcribed. In module A, the interviews will be analyzed with reflexive thematical analysis by Braun and Clark [56]. As already stated, this method is used to understand how interview participants "make sense" of their experiences. This allows insight into tacit changes in self-concepts, implicit values psychosocial demands and resources, and perceived work-related stress. Additionally, it allows to conduct an analysis of themes and content provided by the interview partners. The IOSM team will individually evaluate each interview and compare the interviews to analyze common patterns. To ensure quality control and richness of analysis, each interview will be analyzed by 2 researchers, and preliminary results will be continuously discussed with additional researchers from the joint project. The interviews in module B will be analyzed with reflexive thematical analysis by Braun and Clark [56], as we aim to collect and structure the overarching themes and their various dimensions. The same measures for quality control, as described in module A, will be applied. For additional quality control, a member check with interview participants of phase 4 is planned: preliminary results will be presented, and participants will be invited to give critical feedback, which will be integrated into the further analysis.

Results

The project started in March 2020.

Study Phase 1: Literature Review

The literature review on ethical, legal, social, and systemic impacts of SCAs was completed in December 2021 and will be published in 2022.

Study Phase 2: Cross-sectional Survey of SCA Users and SCA Nonusers

The data collection for study phase 2 was finished in July 2021 (n=1074); the publication of the results is planned for 2022.

Study Phase 3: Diary-Based Self-observation Combined With Semistructured User Interviews

For study phase 3, data collection of the user diaries (n=48) was completed in October 2021, user interviews were conducted in February and March 2022, and publication of the results is planned for 2022.

Study Phase 4: Semistructured Interviews With GPs and Health Care Experts

The recruitment of experts and GPs (study phase 4) is still ongoing and will be finished in 2022.

Discussion

Principal Findings

This protocol describes an interdisciplinary, mixed methods, multiphase research program to comprise the impact of SCAs on the 3 levels (microlevel, mesolevel, and macrolevel) of the health care system [26]. The main findings of the recent exploratory study will be an overview of the ethical, legal, social, and systemic impacts literature on SCAs, epidemiology data of SCAs (as degree of use in Germany, predictors for SCA usage considering user characteristics), requirements of SCA use from a user perspective, a description of SCA user behavior, and a comprehensive assessment of the perspective of GPs and health care experts on SCAs.

Digital health care innovations and their impact on the health care system is a prevailing topic in times of digitalization and the increasing demand of health care professionals such as GPs. In contrast to apps for specialists, user-accessible apps such as SCAs are an unknown variable in the development of health care delivery in the future. Conflicting claims of medical, ethical, and social advantages or disadvantages of SCAs characterize the current state of the debate. Apparently paradoxical effects, as undermining trust in the patient-physician relationship on the one hand, improved exchange on the other hand, may be coexisting or representing different perspectives in scenarios that require further description. The conflicting information about ethical, legal, social, and systemic impacts requires more empiric data to inform and deepen the debate [57].

Little is known about the psychosocial demands and resources of GPs in this context. SCAs are attributed to result in an overuse as well as in an underuse of health care resources. Finally, existing health inequalities may be improved or worsened by their impact. Based on an ScR of the ethical, social, and legal literature, the project will provide evidence, which of these contradicting assumptions is confirmed by the empirical study of the user experiences in the case study at hand. Using SCA as an example of consumer-oriented digital innovations, this study aims to research and integrate questions that are important for the general debate on digital transformation: what is known about the topic? How widespread is the phenomenon? How do users apply the innovation? How does that modulate their behavior and impact their health care usage? How do negotiations with health care providers play out? Which regulatory legislation is necessary? What are the implications for the physicians in particular and the health care system as a whole? However, only collecting data from 1 stakeholder's perspective without considering possible interactions will generate blind spots. Thus, the main challenge is to consider different stakeholders' perspectives, wants and needs, and to engage in a transparent debate on the current dynamic developments.

Strengths and Limitations

The projects' concept integrates different data sources and methods from the very start. The multidisciplinary, multiphase design, and the methods and skills mix of the study partners create a scenario in which methodological strengths are complimentary and perspectives can be negotiated. For example, by limiting recruitment to a single SCA (the Ada app) in the qualitative study phases, we are able to focus the analysis [49]. At the same time, through the representative survey, these qualitative results can be put in a broader context, which will contribute to implications for the health care system. Another strength is the immanent consideration of the user perspective by combining a survey, user diary, and user interviews. In integrating relevant perspectives and plotting study phases to converge in integrated workshops, we present an approach for integrated research in ethics, social, and health sciences. This is possible owing to the long-standing cooperation between all involved partners and previous positive experiences in common projects.

This research project also has limitations: we will not investigate how SCAs perform in terms of medical accuracy. Further, we will not be able to observe direct interaction of patients and physicians in the context of SCAs and see how SCAs influence the patient-physician relationship directly. Moreover, we assessed user and nonuser characteristics through subjective user rating rather than objective measurements (eg, overall health rating of participant). Lastly, we will not directly investigate the effect of SCAs on health care utilization. We will, however, assess parameters considering utilization reported by participants.

Conclusions

This study offers an opportunity for multidisciplinary research: it considers different research perspectives and methodologies from ethics, legal, social, health care, and medical science and integrates them in 1 study process. We are confident that this will lead to new insights for the use of SCAs and digitalization in health care while providing a novel methodological approach for integrated research in health care digitalization.

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Authors' Contributions

AJW and RK equally contributed to the manuscript draft and the writing process. RK, SJ, MAR, UW, HJE, CP, RR, and TH collaborated on the research proposal grant, study protocol, and study design. The authors' contributions to the design of the study phases and the editing of the corresponding phases in the manuscript were as follows: UW, RM, RR, HJE, TH, and MK contributed to study phase 1. AJW, SJ, and RK contributed to study phase 2. Phase 3 was collaboratively contributed to by RK, CP, MK, AJW, and RM. MAR and CP contributed to phase 4A; AJW, RK, and CP contributed to phase 4B. All authors collaborated on the editing of the manuscript draft. All authors approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Evaluated scales that were used in the survey of study phase 2.
[PNG File , 77 KB - resprot_v11i5e34026_app1.png]

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Abbreviations

GP: general practitioner
GRAMMS: Good Reporting of A Mixed Methods Study
IEHM: Institute of Ethics and History of Medicine, University Tübingen
IGP: Institute of General Practice and Interprofessional Care, University Hospital Tübingen
IOSM: Institute of Occupational and Social Medicine and Health Services Research, University Hospital Tübingen
PRISMA-ScR: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews
SCA: Symptom Checker App
ScR: scoping review
SRQR: Standards for Reporting Qualitative Research
STROBE: STrengthening the Reporting of OBservational studies in Epidemiology
TAM: Technology Acceptance Model

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Protocol

The Effects of a Virtual Reality–Based Training Program for Adolescents With Disruptive Behavior Problems on Cognitive Distortions and Treatment Motivation: Protocol for a Multiple Baseline Single-Case Experimental Design

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Abstract

Background: Serious disruptive behavior among adolescents is a prevalent and often persistent problem. This highlights the importance of adequate and effective treatment to help adolescents with disruptive behavior problems react less hostile and aggressive. In order to create a treatment environment in which behavioral change can be enhanced, treatment motivation plays an essential role. Regarding treatment itself, a focus on challenging self-serving cognitive distortions in order to achieve behavioral change is important. Street Temptations (ST) is a new training program that was developed to address both treatment motivation and cognitive distortions in adolescents with disruptive behavior problems. One of the innovative aspects of ST is the use of virtual reality (VR) techniques to provide adolescents during treatment with visually presented daily social scenarios to activate emotional engagement and dysfunctional cognitions. By using the VR scenarios as an integral starting point of ST's sessions and transferring the power of the VR experience into playful and dynamic exercises to practice social perspective–taking, adolescents are encouraged to reflect on both their own behavior and that of others. This focus on reflection is grounded in ST's main treatment mechanism to influence treatment motivation and cognitive distortions, namely, mentalizing (ie, reflective functioning).

Objective: The aim of this study is to describe the research protocol to evaluate the effects of ST on treatment motivation and cognitive distortions. We take a closer look at the use of ST and the methodology used, namely, the repeated single-case experimental design (SCED).

Methods: The effects of ST are studied through a multiple baseline SCED, using both quantitative and qualitative data. In total, 18 adolescents from secure residential youth care facilities and secondary special education schools are randomly assigned to 1 of the 3 different baseline conditions. Throughout the baseline phase (1, 2, or 3 weeks), intervention phase (4 weeks), and follow-up phase (1, 2, or 3 weeks), daily measurements on treatment motivation and cognitive distortions are conducted. Secondary study

parameters are assessed before baseline, after intervention, and after follow-up. Qualitative data are collected after intervention, as well as at 3 months and 6 months after the intervention.

Results: Data collection for this study started in November 2021 and is planned to be completed by August 2023. The results will be published in peer-reviewed journals and presented at national and international conferences.

Conclusions: ST aims to improve the disruptive behavior problems of adolescents. This study will be the first to gain insights into the effectiveness of ST. The strengths of this study include its thorough and individually focused design (SCED), the focus on a residential as well as a secondary special education setting, and the ecological validity. The implications for practice are discussed.

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International Registered Report Identifier (IRRID): PRR1-10.2196/33555

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KEYWORDS

treatment motivation; cognitive distortions; reflective functioning; disruptive behavior problems; adolescence; virtual reality; single-case experimental design

Introduction

Background

Disruptive behavior of young children is among the most frequent reasons for referral to child and adolescent mental health care services worldwide [1]. During adolescence, disruptive behavior continues to be a widely acknowledged problem [2-5]. Disruptive behavior disorders include conduct disorder and oppositional defiant disorder [6]. Behavior that fits the classification of disruptive behavior disorders can be characterized as disobedient, stubborn, irritable, or even hostile and aggressive, and often manifests itself in patterns of uncooperative and defiant behavior [6]. Adolescents themselves are affected by displaying such behavior as well as their surroundings and society as a whole [7-9]. Consistent occurrence of untreated disruptive behavior problems has a wide variety of persistent negative outcomes such as school dropouts, substance use, developing antisocial personality disorders, and both nonviolent and violent delinquency and criminality [7,10-13]. This highlights the importance of adequate and effective treatment for adolescents with disruptive behavior problems in order to help them develop and increase the necessary skills to react in a less hostile and aggressive way.

Well-established, evidence-based treatments for adolescents with disruptive behavior problems, such as the Multisystemic Therapy and Treatment Foster Care Oregon, primarily focus on a small portion of adolescents with disruptive behavior problems, that is, adolescents with judicial involvement within the context of forensic youth care [14]. Compared to more typical disruptive adolescents, this subpopulation of adolescents with judicial involvement tends to show a significantly higher severity of problems and needs [14]. Although well-established treatments aimed at these more severe problems and needs are available, as mentioned, the effects of such programs appear to be smaller than the effects of more preventive programs targeting adolescents at the onset of judicial involvement [15]. In other words, intervening at an earlier stage seems to be more effective than curing at a later stage. It is safe to say that adequate treatment options for adolescents with less severe disruptive behavior problems are also needed in order to prevent the escalation of these problems.

Treatment motivation is considered to be one of the preconditions for treatment to be effective [16,17]. Interventions that theoretically have the right focus may still have difficulty accomplishing progress when adolescents' resistance to treatment is not addressed as well [18]. Motivation and involvement of all key players were also found to be one of the common treatment mechanisms in the evidence-based systemic treatments mentioned above [19]. However, lack of treatment motivation is relatively common among adolescents with disruptive behavior problems [20-23]. Consequently, a focus on intrinsic motivation is an important factor in providing the opportunities for enduring behavior changes in adolescents [24]. By implementing programs or modules that increase adolescents' motivation, the chances of successful treatment can be increased [25]. More specifically, a study by van der Stouwe et al [26] showed treatment motivation to be predictive of self-serving cognitive distortions in a sample of Dutch juvenile delinquents. Juveniles showed better results for these outcomes when their motivation was higher, regardless of the treatment condition.

The self-serving cognitive distortions mentioned above are associated with disruptive behavior problems [27-31]. Cognitive distortions are defined as "inaccurate or biased ways of attending to or conferring meaning upon experiences" [32], because of which problematic emotional responses and behavior can arise [31]. The primary self-serving cognitive distortions, that is, self-centered distortions, indicate that someone considers their own views, expectations, needs, rights, immediate feelings, and desires to be of such importance that someone else's legitimate views (or even one's own long-term best interest) are scarcely considered or disregarded altogether [27]. These primary distortions increase the chance of engaging in disruptive behavior [33]. They are typically accompanied by 3 types of secondary cognitive distortions that function as protective rationalizations against certain types of psychological stress [18,33]. These are categorized as blaming others, assuming the worst, and minimizing or mislabeling [32]. A specific biased

way of attributing meaning that has been given prominent attention in research is hostile attribution bias (HAB) [34]. HAB can be seen as an example of the category assuming the worst [31,32,35]. Research shows that self-serving cognitive distortions and HAB more specifically can improve when targeted during treatment [26,33,36,37].

According to Gibbs et al [18], challenging and encouraging adolescents to put themselves in others' positions directly challenges adolescents' self-serving cognitive distortions as well. Providing social perspective–taking opportunities should thus play a fundamental role when treating adolescents with disruptive behavior problems [18]. Research by Verhoef et al [34] implies that these social perspective–taking opportunities should be primarily targeted at emotionally engaging situations. Their meta-analysis showed that the relation between HAB and aggressive behavior was stronger in social interactions that evoked sufficient emotional engagement. Inhibiting deliberate reflective processing by derailing cognitive processes, the strong emotions may elicit the automatic and emotional processes that activate HAB [34]. When activated, the needed content to work with during treatment sessions emerges.

Taken together, adequate treatment options for adolescents with disruptive behavior problems are needed to prevent escalation of their problems. Treatment motivation is an important requisite to increase the chances of successful behavior change. In terms of content, emotionally engaging social perspective–taking opportunities can challenge self-serving cognitive distortions and in that way induce behavioral change.

Street Temptations

Street Temptations (ST) is a new and innovative training program that was developed by Garage2020 in cocreation with Levvel, a secure residential facility and youth care provider in Amsterdam, The Netherlands, to influence treatment motivation as well as cognitive distortions of adolescents with disruptive behavior problems. In order to achieve this effect, ST's exercises focus entirely on social perspective–taking opportunities. ST specifically aims to work with scenarios that are emotionally engaging, as this is the type of situation that should be focused on in treatment [34]. To create these scenarios, ST uses the potential of virtual reality (VR).

The term VR indicates a replacement of the physical environment by a 3D computer or an artificially generated interactive environment [38]. When done right, VR has the power to achieve full immersion and presence [39,40]. Immersion refers to the degree to which a user is aware of the real world while in the VR environment. Presence refers to "the psychological state in which a participant accepts, interacts, and is physically, socially, and emotionally engaged in the virtual world" [41]. Put otherwise, presence causes the subjective sense of "being there" [42,43]. Together, immersion and presence will let the human brain treat a VR experience as psychologically real, letting users react toward the VR experience as if it were real [39]. In this way, VR ensures there is less of a demand on the cognitive abilities needed to make a realistic representation of a hypothetical situation [44]. This makes VR ideally suited to meet the needs of the adolescents with disruptive behavior problems aimed at, considering that mild-to-borderline intellectual disabilities are not uncommon within this target population [45,46]. Visual support is highly recommended when treating children and adolescents with mild-to-borderline intellectual disabilities [47]. Consequently, this innovative feature can provide the necessary emotional engaging scenarios for social perspective–taking challenges. Additionally, with VR, it is possible to create realistic and recognizable scenarios that in the real world would be impossible or unethical to create [39]. The power of the VR scenarios is extended in playful and dynamic exercises. By providing therapists with practical tools, they are enabled to encourage adolescents to reflect on both their own behavior as on that of others.

The focus on reflection is grounded in the assumably main therapeutic mechanism of ST, that is, mentalizing. The concept of mentalizing, operationalized as reflective functioning, refers to "the mental process by which an individual implicitly and explicitly interprets the actions of himself or herself and others as meaningful on the basis of intentional mental states such as personal desires, needs, feelings, beliefs, and reasons" [48]. Through this mental process, people can make sense of their social world, making mentalization a core aspect of human social functioning [49]. Research shows that many adolescents with disruptive behavior problems have difficulty mentalizing [50]. Mentalizing problems cause difficulties in predicting and anticipating the behavior and motives of others [51-53]. Problems regarding self-awareness and self-regulation are likely to occur as well [49]. Consequently, the risk of misunderstanding social cues and impulsive actions within the context of interpersonal communication increases [50]. An empirical evaluation by Bo et al [54] shows that the mentalizing abilities of adolescents with diagnosed borderline personality disorder can significantly improve over the course of mentalization-based treatment.

Since ST is a newly developed program, so far, only test runs regarding the feasibility and potential of the program have been conducted [55]. Owing to the importance of adequate treatment programs for adolescents with disruptive behavior problems as well as creating the conditions under which the likelihood of successful treatment increases, more extensive research into the value and effectiveness of ST is needed. The aim of this study is to describe the repeated single-case experimental design (SCED) that is used to provide a first and thorough exploration into ST's effectiveness.

Methods

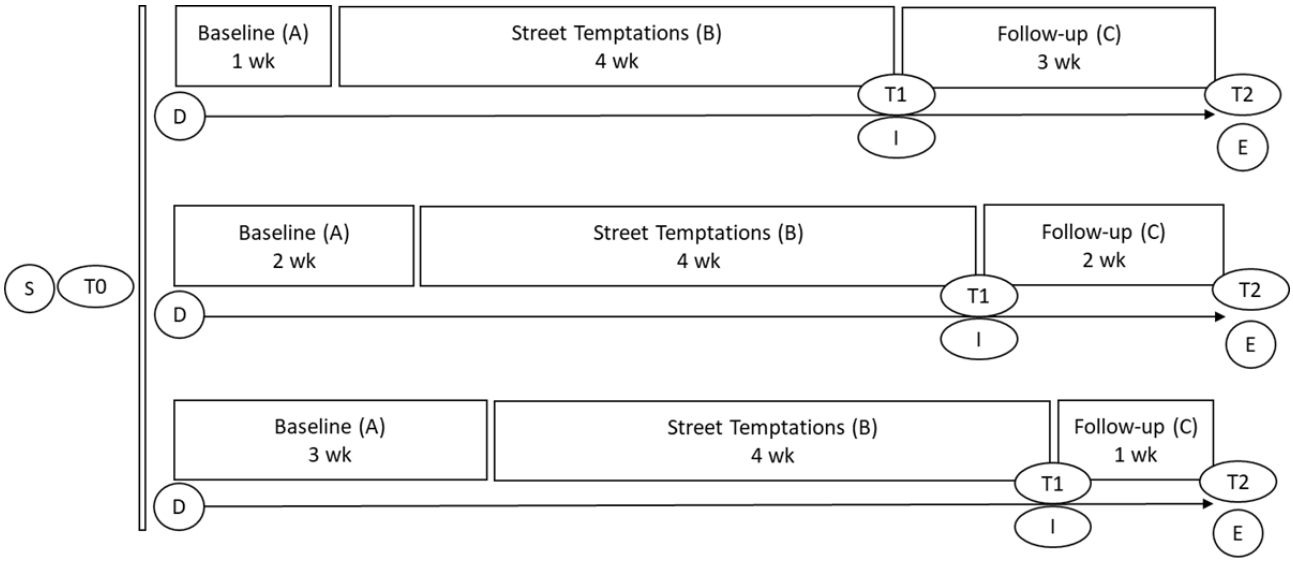
Design

This study applies a randomized, nonconcurrent, multiple baseline SCED across single participants [56,57]. As compared to group-comparison designs where experimental units refer to groups of participants assigned to different conditions, the experimental units in SCEDs are formed by repeated measurements within an individual [58]. In a multiple baseline SCED, repeated measurements are conducted both in the absence and in the presence of a certain treatment. This allows participants to serve as their own controls [59]. Well-designed and well-executed SCEDs are able to determine whether a causal

relationship exists between an intervention (ie, an independent variable) and change in an outcome measure (ie, a dependent variable) [60]. SCEDs can be particularly useful in the early developmental phase of research, whereby unforeseen adjustments can be implemented immediately [59,61]. Additionally, SCEDs allow tailoring the intervention to the unique needs of participants. SCEDs also lend themselves very well for research in clinical settings, with small and heterogeneous populations that are difficult to capture in more standard group designs such as randomized controlled trials. The population ST focuses on can be characterized as such a population. Moreover, the intense and comprehensive studying of a small number of participants allows better knowledge of the studied individuals, insight into possible mediation effects, and the detection of intervention effects within the variability of participants' performances [62].

Participants are randomized to a 1-, 2-, or 3-week baseline phase. Randomization to varying baseline periods enables us to determine whether change in measurements is exclusively related to the application of the intervention. The random assignment is similar to the way in which a random assignment is used in between-participants designs [58]. The length of the phases has been chosen to keep them as short as possible in order to prevent dropout of the already difficult-to-reach target population. To assess primary outcomes, participants complete repeated measurements during a baseline phase (phase A), an intervention phase (phase B), and a short-term follow-up phase (phase C). These measurements are administered electronically once a day using a smartphone app. Phase A acts as a control and is therefore compared to phases B and C. To assess secondary outcomes, pre-(T0), post-(T1), and short-term follow-up measurements (T2), as well as qualitative data collection are used within the SCEDs. In total, the research period from the start of the baseline until the end of the short-term follow-up takes up approximately 8 weeks per participant. In addition to the short-term follow-up, qualitative data are also collected at 3 months and 6 months after T2. An overview of the study design is shown in Figure 1.

Figure 1. Overview of the study design with 3 different conditions. The daily repeated measure starts directly after T0, on the same day. Moreover, 3 and 6 months after T2, adolescents are approached again to participate in follow-up interviews. D: daily repeated measure; E: end of daily measure study period; I: first interview with adolescents and trainers; S: start of the study, application, informed consent, and eligibility check; T0: pretreatment assessment and randomization; T1: posttreatment assessment; T2: short-term follow-up assessment; wk: week.



Participants

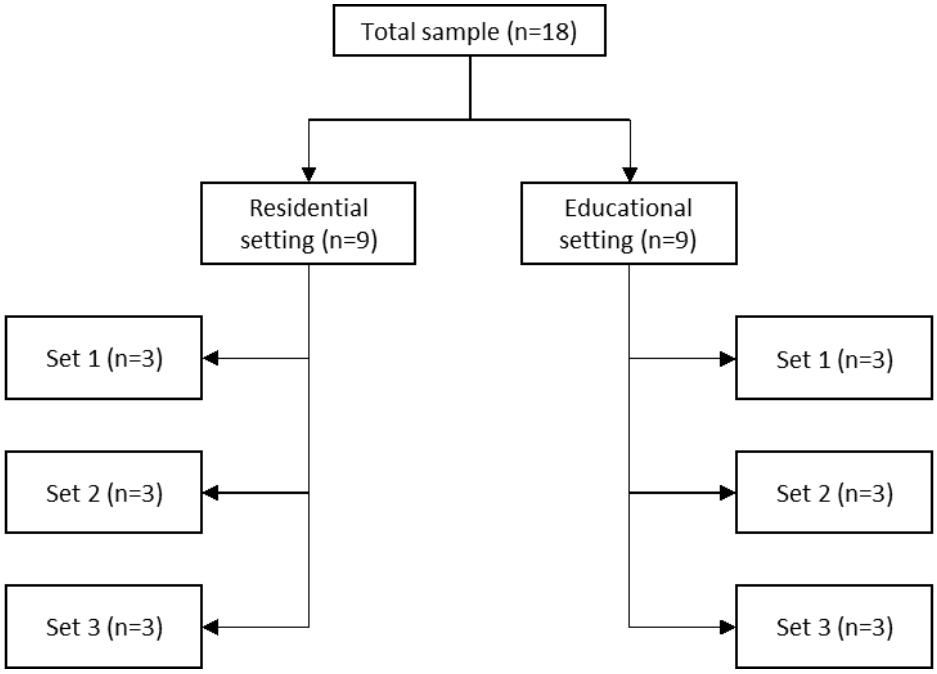
Participants are recruited among adolescents from secure residential youth care facilities and secondary special education schools in the Netherlands. Both populations are characterized by serious externalizing problems. These problems are often accompanied by internalizing problems, sometimes in combination with psychiatric and addiction problems. Adolescents who meet the following criteria are eligible for inclusion: (1) aged between 12 and 18 years, (2) antisocial or externalizing behavioral problems, (3) deficits regarding cognitive distortions or treatment motivation, (4) presence or risk of delinquent behavior, (5) assigned to ST after multidisciplinary consultation, (6) expected stay of at least 2 months, and (7) basic understanding of mobile apps. A potential participant who meets any of the following criteria is excluded from participation: (1) severe physical impairment such as deafness and blindness, (2) severe psychiatric problems such as psychosis or high risk of suicide requiring immediate intervention, (3) trauma from serious violence, (4) epilepsy or serious problems regarding motion sickness, and (5) insufficient understanding of the spoken and written Dutch language.

Sample Size

According to SCED research standards, SCEDs need at least 3 attempts to demonstrate an intervention effect. Each of these attempts needs to be at a different time point, requiring a multiple baseline SCED to have at least 3 baseline conditions. Additionally, each phase must include a minimum of 3, preferably 5, data points to qualify as an attempt to demonstrate an effect [59,63,64]. Regarding treatment attrition, a meta-analysis on inpatient juvenile offender treatment showed attrition rates of up to about 60% [17]. A study on residential treatment for adolescents with serious disruptive behavior problems reported that 51% had left the treatment center prematurely [65]. In order to adhere to the stated minimum of

3 participants by SCED research standards, while compensating for a potential 60% attrition rate, a total of 18 participants is strived to include in the study. The 18 participants are equally divided over the 2 research settings and the 3 baseline conditions. In combination with the daily repeated measurements, this sample results in 6 initial attempts to demonstrate an intervention effect of ST. An overview of the sample distribution is displayed in Figure 2. Each set consists of the 3 baseline conditions shown in Figure 1.

Figure 2. Overview of the sample distribution.



Procedures

Within the residential facilities, all referred adolescents are screened by the clinicians and ST trainers. Regarding the participating schools, adolescents from selected classes are screened during the first few weeks of the new academic year. This screening process is chosen to minimize the risk of nonresponse. Screening is only done by the professionals from the facilities and schools. All professionals involved are extensively briefed on the population the study focuses on. When an adolescent is thought to be eligible to participate in the study, the professional informs the adolescent about the study. The adolescent is shown a short video, in which the researcher briefly introduces herself and the project. Written information is provided as well. When the adolescent is interested to participate and gives oral permission to be approached, the researcher plans an informed consent appointment. Written informed consent is signed when the adolescent agrees to participate in the study. In the case of a minor, parents or a legal guardian signs a written informed consent as well. Adolescents that do not agree to participate in the study do not start with ST and receive treatment as usual.

After the informed consent procedure, the researchers decide whether a participant is eligible to take part based on the inclusion and exclusion criteria. When necessary, a clinician will be consulted to make an informed decision. After official enrollment, premeasurements are conducted, and randomization takes place. Because trainers, clinicians, and adolescents will notice in which condition adolescents are participating, allocation is not blinded. Appointments for the ST-intake session and following sessions are made according to the randomization.

Directly after the premeasurements have been conducted, the daily measurements are set up by installing the data collection app (m-Path). Everything about the app and data collection is explained as well as tested with the adolescent. From then on, the app automatically sends out notifications for the daily assessments within set time frames. This continues until the last day of the follow-up phase, according to the randomization. During the baseline and intervention phase, the researcher, ST trainers, and participants are in touch on a regular basis. Together, they check how things are going and whether there are any particularities regarding ST, the daily measurements, or in general. The intensity (eg, frequency, duration) of these contact moments will be kept the same across participants as much as possible. If necessary, for example, to encourage participants to fill in their daily measurements, the researcher will be in touch more often. Contact moments will be registered per participant in order to take possible variations regarding contact moments into account when analyzing treatment effects.

ST trainers inform the researcher when the last ST session takes place. After the last session has taken place, 2 appointments are scheduled with the participating adolescent: 1 for the posttreatment assessment and 1 for the interview. This is done separately in order to reduce the burden on the adolescent. Additionally, 1 appointment is scheduled with the ST trainer for the interview with the trainer. After the last ST session, participants enter the follow-up phase. The researcher schedules the last appointment at the end of this phase to conduct the follow-up measurements and to close the study period together with the ST trainer and participant. At 3 months and 6 months after the end of the study period, the adolescents are approached again to participate in the 2 additional follow-up interviews.

When a participant decides to leave the study prematurely, it is possible to finish the remaining ST sessions. The decision to do so or not will always be made in consultation with the trainer and clinician. Owing to the inevitable heterogeneity with regard to both the problems of the adolescents as well as the moment at which they participate in ST within their treatment process, no restrictions are imposed with regard to cointervention.

ST Sessions

ST consists of seven 45-60-minute sessions. During the sessions, input and direction from the adolescents form the main lead regarding the exercises to offer adolescents a creative and alternative way to develop certain skills and to freely share their personal story. In this way, ST aims to add to more traditional modes that are not always tailored to the needs of adolescents [66]. This adheres to adolescents' need for autonomy and control regarding their treatment [67]. Adolescents underscore their own voices and contributions as essential for successful therapy in order for therapists to really get to know their personal stories [68].

By incorporating mentalizing as the main therapeutic mechanism, ST aims to influence both treatment motivation and cognitive distortions. In order to develop the needed motivation to engage in treatment for behavioral change, it is in the first place necessary to acknowledge problematic behavior and to seek help for this behavior [69]. Additionally, someone must have the desire to behave more socially adequate and to formulate the kind of person someone would want to be in the future. Clustering these factors, te Velde et al [70] describe self-reflection as an important concept regarding treatment motivation. Since self-reflection is part of the definition of mentalizing, it is plausible that mentalizing can function as a therapeutic mechanism regarding treatment motivation. Besides, social perspective–taking is an important component of mentalizing [71]. By centering the exercises around that component, the incorrect or biased ways of attending or conferring meaning upon experiences (ie, the cognitive distortions) can be challenged [18]. Given its definition, the act of mentalization reflects the way in which an individual can give meaning to social experiences, namely, on the basis of inner mental experiences. By giving that way of meaning making a central role within the exercises and thereby helping adolescents improve the way they can make sense of their social world, mentalizing can function as a therapeutic mechanism regarding cognitive distortions as well.

The sessions are divided over 2 modules, A and B, which are executed in a fixed order. Before starting with the first module (ie, A), there is an intake session during which the adolescent chooses a personal learning goal. This goal focuses on mentalizing abilities, for example, "I want to learn that how I see a situation doesn't have to be the same as how somebody else sees the same situation" or "I want to learn to listen to what somebody else thinks, feels, or would want to do in a situation so that I can better understand that person." Each consecutive session ends with discussing the personal learning objective.

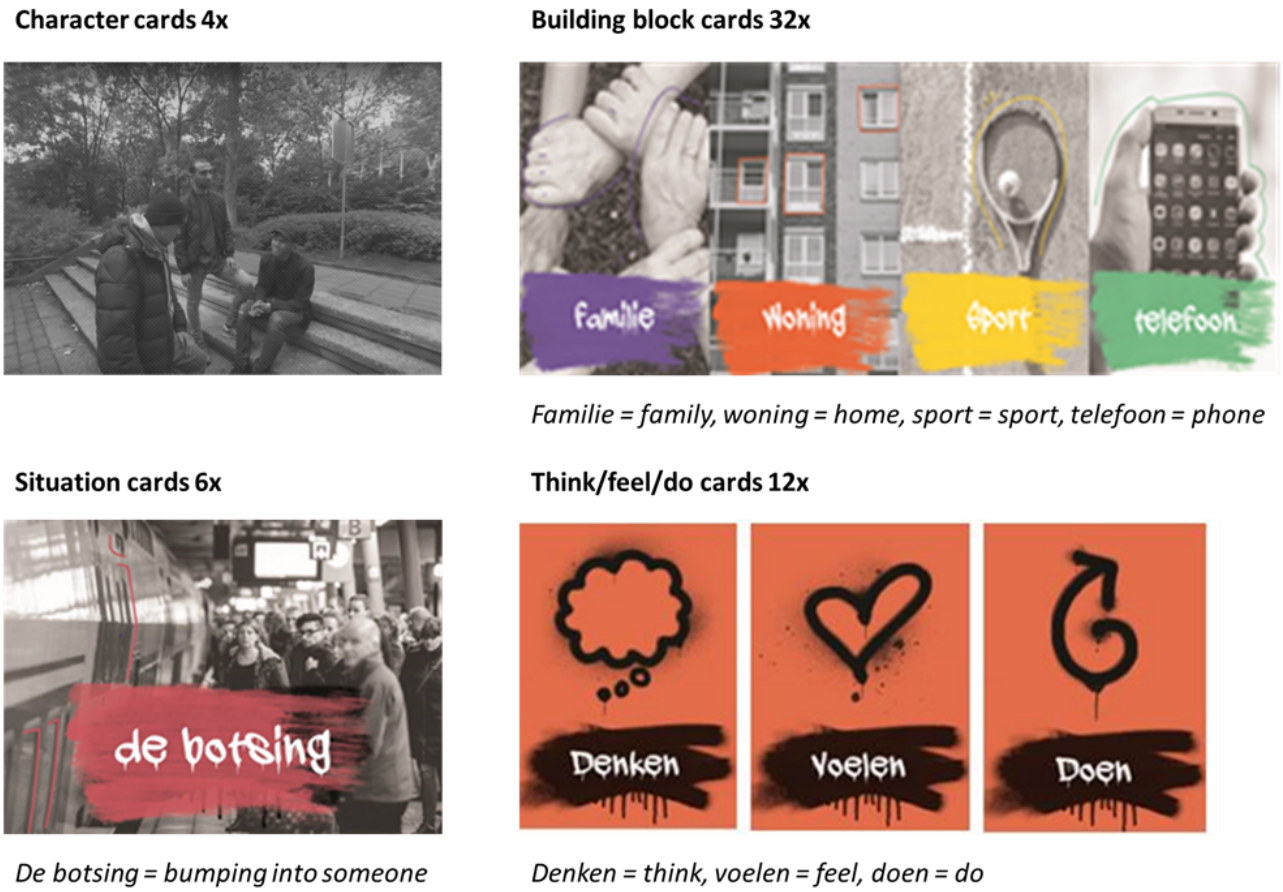
Modules of the Sessions

Module A

Module A revolves around 3 main characters. Each session starts with watching a 360° VR video. This video (see Figure 3) is used to present the scenario and characters on which the exercises are based. The video shows a small group of guys in a park. Youngster 1 forces youngster 2 to beat up a passerby, youngster 3, and youngster 2 obeys. In between, there are fragments shown in which youngster 2 is interviewed about why he knocked down youngster 3. The video ends with a compilation of videos from the internet of real fights between adolescents. During watching, the video is streamed from the VR glasses to an extra screen, allowing the trainer to see what the adolescent is watching simultaneously. After watching the video, the adolescent chooses one of the 3 characters to focus on that session. Together with the trainer, the adolescent creates a backstory for the character based on various building block cards (see Figure 4), for example, for family, living situation, and sports. When the character has been given a personal story, the adolescent takes on the character's perspective. Based on that perspective, linked to the created personal story, the trainer challenges the adolescent to reflect on the scenario from the video. After that, the adolescent switches back to their own perspective to discuss the differences and similarities between the 2 perspectives and why those might be present. Apart from watching the VR video, the exercises are performed outside of the VR environment. Figure 4 shows examples of the different cards that are used.

Figure 3. Screen capture of the virtual reality video.

Figure 4. Examples of the cards used in the sessions.



Module B

In module B, the exercises revolve mainly around a personal experience chosen by the adolescent. Adolescents visualize the scenario of this situation for the trainer by using Street View VR, which means that the adolescent will use the VR glasses to virtually go to the place of their personal experience. While virtually being present in that place, the trainer watches along with the stream of the VR glasses and the adolescent explains what exactly happened in that place. Thereafter, the same perspective-switching exercises as described above are executed but with different perspectives. One session is about the perspective from an unknown passerby, and the other session is about the perspective from someone in the social network of

the adolescent. In an additional exercise, a fictional character is created. This character is put in different situations based on the situation cards, and the adolescent has to make and substantiate a choice in that situation based on the character. As in module A, in module B, all exercises take place outside of the VR environment as well. The use of VR serves to present a scenario on which the exercises will be based. During the last session, the trainer and adolescent reflect on the progress that has been made regarding the personal learning goal. They also evaluate the program all together and what the adolescent has learned in addition to the set learning objective. It is possible to involve, for example, the mentor in this final session and have the adolescent explain what has been done and learned.

Training and Supervision

ST trainers receive a 2-day training course, provided by the first author and a highly experienced psychotherapist who is also a registered teacher and supervisor. The training focuses on the theoretical background of ST, working with VR, the ST protocol, and practicing the learned skills by participating in and reflecting on role plays with experience experts. In addition to the training, ST trainers are guided throughout the research period by participating in monthly supervision sessions. These sessions are also facilitated by the first author and the clinician from the ST training. Besides the supervision, trainers are encouraged to engage in peer consultation. Lastly, they are able to receive telephonic consultation by the first author or clinician on request. To gain insight into the extent to which trainers commit to the protocol, trainers are required to fill out session forms.

Measures

Primary Outcome Measures

The main study parameters are assessed once a day in the format of an idiographic digital self-report questionnaire for the adolescents. The items are based on the questionnaires that are assessed at T0 and will be presented in a random order each day.

Treatment Motivation

Treatment motivation is measured using the Dutch Adolescent Treatment Motivation Questionnaire (ATMQ) [72]. The ATMQ consists of 11 self-report items with a 3-point Likert scale, ranging from “not true” to “true.” Reliability and validity proved to be good [72]. For the daily questionnaire, the ATMQ is included as a whole.

Cognitive Distortions

Cognitive distortions are assessed using the self-report How I Think questionnaire (HIT) [32]. The HIT contains 54 six-point Likert items that vary from “totally agree” to “totally disagree.” The Dutch version of the HIT showed acceptable reliability and validity [31,73]. To create the daily questionnaire, the subscale with the highest score will be selected.

Secondary Outcome Measures

The secondary study parameters include change in reflective functioning and social perspective–taking as well as a qualitative exploration of the overall experiences with regard to ST and VR.

Reflective Functioning

Reflective functioning is measured using the Reflective Functioning Questionnaire for Youths (RFQY) [74] and the Self-Reflection and Insight Scale for Youth (SRIS-Y) [75]. The RFQY is a 46-item self-report measure scored on a 6-point Likert scale ranging from “strongly disagree” to “strongly agree.” The questionnaire is adapted from the adult version, the Reflective Functioning Questionnaire [76], by rewording some items for a better developmental match. Both studies report preliminary support regarding reliability and validity. The RFQY consists of 2 scales, with a total RFQY score deriving from the sum of both scale scores. Higher scores indicate greater capacity for reflective function. The SRIS-Y is a 17-item, self-report questionnaire, answered on a 6-point Likert scale ranging from “disagree strongly” to “agree strongly.” The instrument consists of 2 subscales, Self-Reflection and Insight, resulting in 2 separate scores. The original adult version is reported as a reliable and valid measure of self-reflection and insight in adults [77]. Likewise, the SRIS-Y appears as a developmentally appropriate and psychometrically sound measure of self-reflection and insight in adolescents [75].

Social Perspective–Taking

Social perspective–taking is assessed using the Perspective Taking subscale of the Interpersonal Reactivity Index [78,79]. The Perspective Taking subscale consists of 7 items, answered on a 5-point Likert scale. The Dutch version of the Interpersonal Reactivity Index appears to be a psychometric adequate instrument [80].

ST Evaluation

The ST evaluation is done by conducting semistructured interviews with adolescents as well as trainers based on the Change Interview [81]. The purpose of the Change Interview is to obtain information about clients’ understanding about what has changed during therapy, why those changes have occurred, and what factors might have gotten in the way of change. By obtaining this information regarding ST, the interviews enable learning whether and, if so, what changes have occurred throughout ST from the adolescents’ and trainers’ perspectives. In addition, adolescents and trainers can clarify why they think those changes have occurred, referring to both therapy and extratherapy factors. Lastly, important information about hindering factors or possible negative changes regarding ST is gathered.

VR Evaluation

The VR evaluation is done by adding questions regarding this topic to the above-described interviews. All respondents are asked to reflect on their experience with VR in general and working with the VR material, what they believe VR did or did not add to ST, and what they think of the video used in ST. Additionally, they are asked how they think the VR component could be improved.

Sociodemographic Parameters

Sociodemographic information such as age, sex, education level, ethnicity, living situation, and possible experience with minor criminal activity is collected using a demographic questionnaire developed by the researchers. Information regarding diagnostic background and treatment history is collected using file information. When recent IQ data are missing, the Screener for Intelligence and Learning Disabilities [82] is administered.

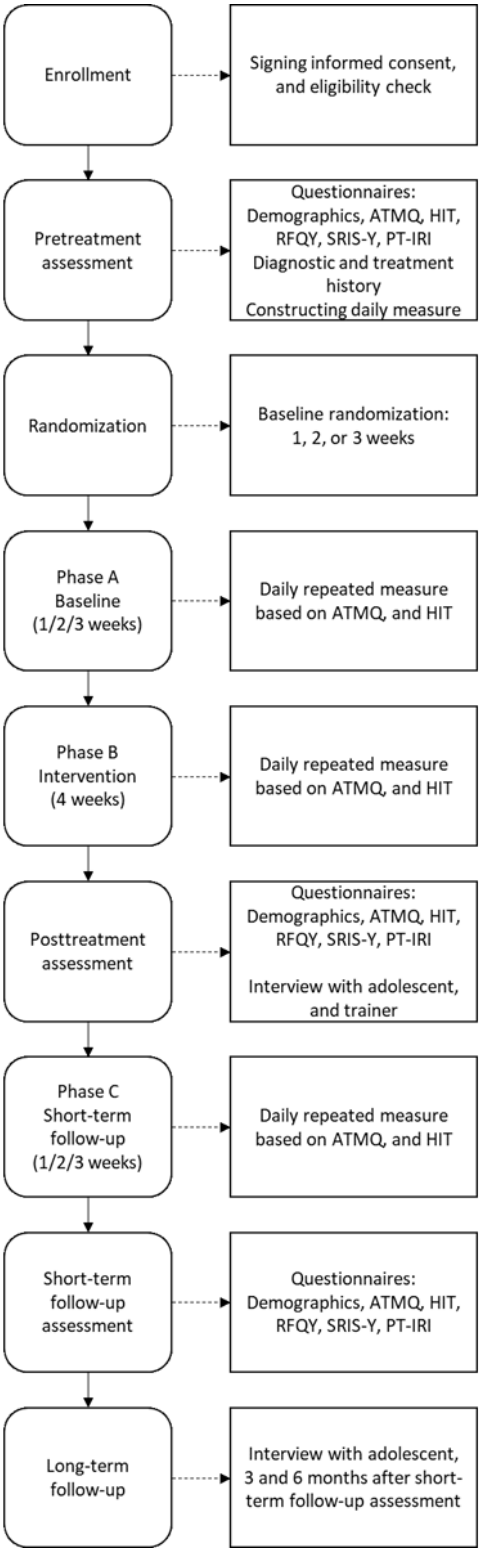
An overview of all the measurement tools and data collection moments is given in Table 1 and Figure 5.

Table 1. Overview of the measurement tools and informants.

Variable	Measure	Informant
Primary outcomes		
Treatment motivation	ATMQ[a]: Daily questionnaire	Adolescent
Cognitive distortions	HIT[b]: Daily questionnaire	Adolescent
Secondary outcomes		
Reflective functioning	RFQY[c], SRIS-Y[d]	Adolescent
Social perspective-taking	PT[e]-subscale	Adolescent
ST[f] evaluation	Semistructured interview	Adolescent, trainer
VR[g] evaluation	Semistructured interview	Adolescent, trainer
Other variables		
Demographics	Questions	Adolescent, clinician
Diagnostic and treatment history	File information	Clinician
Intelligence	File information, SCIL[h]	Clinician, adolescent

[a]ATMQ: Adolescent Treatment Motivation Questionnaire.
[b]HIT: How I Think questionnaire.
[c]RFQY: Reflective Functioning Questionnaire for Youths.
[d]SRIS-Y: Self-Reflection and Insight Scale for Youth.
[e]PT: Perspective Taking.
[f]ST: Street Temptations.
[g]VR: virtual reality.
[h]SCIL: Screener for Intelligence and Learning Disabilities.

Figure 5. Overview of the data collection moments. ATMQ: Adolescent Treatment Motivation Questionnaire; HIT: How I Think questionnaire; IRI: Interpersonal Reactivity Index; PT: Perspective Taking; RFQY: Reflective Functioning Questionnaire for Youths; SRIS-Y: Self-Reflection and Insight Scale for Youth.



Analysis

The primary outcome measures are the daily self-reported questions regarding cognitive distortions and treatment motivation. The resulting data will be presented as quantitative data. Within the context of SCED, including the multiple baseline design, the primary method for data evaluation regarding these repeated measurements is visual analyses [56,57]. This means that within-participants and between-participants data will be visualized graphically in order to explore the level and rate of change between the different phases. The slopes of the variables during the intervention phase will be compared to those of the baseline and follow-up data. The overall pattern in the data will be analyzed by examining whether scores overlap across phases. In order to evaluate the

reliability of potential changes, 95% confidence intervals will be calculated for each participant by using standard errors of difference. Further, a standardized mean difference effect size will be calculated for each outcome variable, using "d-statistics" for SCEDs [83]. Additionally, repeated measures analyses will be conducted. Other procedures for SCEDs will be considered if necessary. The secondary outcome measures consist of the quantitative pre-, post-, and follow-up measurements as well as the semistructured interviews conducted during posttreatment assessment and long-term follow-up. The quantitative data will be analyzed by computing a Reliable Change Index for each measure [84]. Qualitative data will be analyzed using iterative thematic analysis [85]. The interviews will be recorded using professional recording equipment in order to transcribe and analyze the data. A statistics expert of the Clinical Monitoring Center of the Amsterdam University Medical Centers (Amsterdam UMC) will be consulted regarding data analysis.

Ethics Approval and Confidentiality of Data

Ethics approval for this study was obtained in June 2021, which was granted by the independent Medical Ethical Committee of Vrije Universiteit medical center (reference number: 2021.0114). This study will be conducted according to the principles of the World Medical Association Declaration of Helsinki [86] and in accordance with the Medical Research Involving Human Subjects Act. Handling and storage of data will be done in accordance with the General Data Protection Regulation. Collected research data within this study includes questionnaires and interviews, collected by the researchers from the Department of Child and Adolescent Psychiatry at the Amsterdam UMC. All data will be deidentified by giving every participant a unique participant ID. All data from the daily questionnaires, that is, questions and answers, are stored in a protected folder on the phone of the participant. This folder can only be accessed by the m-Path app, not by any other app. An application-layer encryption is applied to the data, meaning that the stored data itself consist of bytes without meaning. The data from these questionnaires will be transferred to the electronic case report form, captured in a custom-made Castor Electronic Data Capture database. Data from the other questionnaires will be directly collected in this database. Physical documents, for example, signed informed consent forms will be stored safely at the Department of Child and Adolescent Psychiatry at the Amsterdam UMC (location Academisch Medisch Centrum). The recordings of the interviews are stored on a protected hard disk. Research data and analyses will be stored for 15 years after finishing the research project in accordance with the Board of Directors of the Amsterdam UMC.

Results

Participant recruitment was started in November 2021. Data collection for this study is expected to be completed by August 2023. Analysis will be conducted after data collection has been completed. The results will be published in peer-reviewed journals and presented at national and international conferences.

Discussion

Aims of the Study

In order to help adolescents with disruptive behavior problems develop and increase the necessary skills to react less hostile and aggressive, challenging self-serving cognitive distortions and enhancing motivation for behavioral change seem particularly important to focus on in treatment [16-18]. In this study, we have elaborated the protocol of the SCED study designed to explore ST's effectiveness—an innovative and dynamic training program that aims to address both the mentioned focus points. Using a repeated multiple baseline SCED, we will examine the effects of participating in ST in both secure residential facilities as well as in secondary special education schools. By conducting this study, we aim to contribute to the adequate and effective treatment of disruptive behavior problems by using new and innovative treatment approaches.

Strengths and Challenges

Our study has multiple strengths. First, by using a SCED instead of a more traditional group comparison design, a lot of individual information is collected throughout the entire treatment process while respecting each participants' personal variability [62]. This ensures that we can gain insight into how each individual trajectory develops, allowing us to indicate for whom and under what circumstances ST is or is not of added value. Second, because the experimental units in our design are the repeated measurements within each individual adolescent instead of groups of adolescents, we are able to tailor the intervention to each adolescent's unique needs [59,61]. This is in line with the stated importance of client-centered approaches and individually tailored treatment [68,87,88]. Third, this study does not only focus on the intensive treatment setting of secure residential care but also looks at the effects within the educational setting. Thus, this study can contribute to the essential prevention and intervention strategies in educational systems with regard to forensic youth care [89]. Overall, the use of the described design allows us to conduct thorough experimental research in the real-life circumstances of everyday clinical practice [60]. In this way, we are able to investigate the effectiveness of ST rather than the efficacy. This is an important distinction, as an efficacious intervention does not necessarily represent an effective intervention in clinical practice. Likewise, an effective intervention in clinical practice may be a less efficacious intervention in the context of scientific research [90]. Investigating ST's effectiveness contributes to the ecological validity of our study.

In addition to the strengths, our study also poses several potential challenges. First, ST is a newly developed intervention that has not been implemented yet. We are therefore dependent on the willingness of organizations to participate and the capacity available to carry out ST in addition to the standard care that is provided. Owing to the hectic work environment of both residential care and special education settings, it may be difficult for organizations to find the time and energy to participate. To increase our chances of success, we focus on the participation of multiple organizations and locations so that our dependency

is not too vulnerable. Second, although we deliberately chose a design that requires a relatively small sample size, nonresponse and dropouts are still realistic challenges. We focus on a hard-to-reach sample, and data collection demands a lot from the participating adolescents. We have tried to reduce the required effort from participants by making the daily measurement as short and easy as possible. Additionally, personal reminders will be used when assessments are not completed, and we will be in touch with participants regularly in order to keep them motivated. Third, although they are validated measures, we only use self-report questionnaires regarding the quantitative measurements. This may cause social desirability bias as well as compromise validity. However, we do use a mixed methods approach as we combine our quantitative measures with qualitative data collection. This triangulation helps us to improve the interpretation of the results and decreases the deficiency of only using self-report [91].

Implications for Practice

ST is a new, innovative training program that specifically aims to meet the needs of adolescents by, among other things, integrating the potential of VR in the exercises. When the results are positive, ST can be further developed, implemented, and researched. In addition, when our described SCED proves to be viable for research in clinical practice, this will enhance the possibilities of clinical research. Adolescents with disruptive behavior problems usually form a hard-to-reach population, which is not easily captured in larger group designs such as randomized controlled trials. This often results in studies that are difficult to conduct, with high risks of, for example, not meeting the required sample size. This study may show alternatives for conducting good scientific research in hectic clinical environments. In this way, our study can provide both a contribution to science as well as to clinical practice.

Conclusions

To date, no research has been conducted into the effectiveness of ST. Our study will be the first to gain insights into the value of ST in helping adolescents with disruptive behavior problems react less hostile and aggressive. Based on the results, ST can be further developed. In addition, the foundation that will be laid with this study allows us to design follow-up studies, for example, to compare the effectiveness of ST with other treatments.

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Authors' Contributions

REKS conceptualized and designed the final study protocol. AP was a major reviewer, and RJLL and LVD reviewed the final study protocol. REKS took the lead in writing the manuscript. All authors read, edited, and approved the final manuscript.

Conflicts of Interest

Garage2020, where REKS and LVD are affiliated with, developed Street Temptations and an educational program for professionals to learn about the scientific and practical background of Street Temptations.

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Abbreviations

ATMQ: Adolescent Treatment Motivation Questionnaire
HAB: hostile attribution bias
HIT: How I Think questionnaire
RFQY: Reflective Functioning Questionnaire for Youths
SCED: single-case experimental design
SRIS-Y: Self-Reflection and Insight Scale for Youth
ST: Street Temptations
VR: virtual reality

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Protocol

Implementation of Virtual Reality to Parent-Child Interaction Therapy for Enhancement of Positive Parenting Skills: Study Protocol for Single-Case Experimental Design With Multiple Baselines

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Abstract

Background: Disruptive behavior is a common reason for young children to be referred to mental health care services worldwide. Research indicates that treatments for child disruptive behavior where parents are the primary agents of change are most impactful. Parent-Child Interaction Therapy (PCIT) is an effective parent management training program currently implemented in therapeutic settings within the Netherlands. Ongoing research into improving the effectiveness of PCIT is being done within these settings. To further promote the key elements of PCIT, this study focuses on creating the opportunity for parents to practice positive parenting skills more outside of the clinical setting by adding virtual reality (VR) as an additional homework element. PCIT has shown to make impactful long-term improvements in parental warmth, responsiveness, and the parent-child relationship. Through VR, parents practice the taught parenting skills out loud in the comfort of their own homes in VR scenarios. We expect that VR addition will innovatively increase the effectiveness of PCIT.

Objective: This study aimed to evaluate the added value of VR to PCIT by using a multiple baseline single-case experimental design (SCED). We expect to find that PCIT-VR will ameliorate positive parenting skills. By implementing the VR element, we secondarily expected that meeting the skill criteria will be achieved sooner, treatment completion rates will increase, and the parent-child relationship will be better, whereas parental stress and child disruptive behavior will decrease.

Methods: A total of 15 children (aged 2-7 years) with disruptive behavior and their parents will be followed throughout the PCIT-VR treatment. Using a multiple baseline SCED with 3 phases, 15 families will fill out questionnaires weekly, in addition to having pre- and posttreatment and follow-up measurements to monitor their positive parenting skills, child disruptive behavior, parenting stress, and VR progress. Moreover, quantitative information and qualitative interviews will be analyzed visually and statistically and summarized to provide a complete picture of experiences.

Results: As of February 2021, 6 families have been enrolled in the study at the moment of submission. Data collection is projected to be completed in 2023. Quantitative and qualitative results are planned to be published in peer-reviewed journals, as well as being presented at national and international conferences.

Conclusions: The SCED—with its phased design, randomization, and the opportunity to replicate and assess both individual and group treatment effects—and adaptability of the VR technology are the strengths of the study. The risks of increased type I errors, maturation effects, or technological failure will be mitigated with the right statistical support. This study aims to magnify the scope of the treatment through additional skill training, ultimately in support of routinely implementing VR within PCIT.

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KEYWORDS

PCIT; virtual reality; single-case experimental design; positive parenting skills; disruptive behavioral problems; parenting; child; disruptive behavior; behavioral; mental health; mobile phone

Introduction

Background

Disruptive behavior is one of the most frequent reasons for young children to be referred to child and adolescent mental health care services worldwide [1]. Statistics show that of the population in the United States, 7% to 9% of children have a diagnosed behavioral problem [2], and in Western culture, there is an increase in the prevalence of behavioral problems [3]. Behavioral problems at a young age have an effect on the child, as well as on his or her surroundings and society at large [4,5]. The long-term effects of untreated, externalizing, disruptive behavior includes school dropouts, peer rejection, developing antisocial personality disorders, higher public costs for health care and education, and both nonviolent and violent delinquency and criminality in adulthood [6-10]. However, protective factors include enhancing prosocial skills for children and fostering the mental well-being of parents [11]. Therefore, to prevent child disruptive behavior or intervene at an early stage, children need evidence-based programs that focus on ameliorating parental skills and diminishing child disruptive behavior. Research concludes that treatments for child disruptive behavior where parents are the primary agents of change have the most substantive evidence for effectiveness [12].

There are currently a few parent management training (PMT) programs that focus on improving parent-child interactions, which are being implemented worldwide [13]. Importantly, parenting is fundamentally linked to children developing life skills, and worldwide research into parenting programs has shown that developmental, emotional, behavioral, and health outcomes for both parents and children can improve as a result [14]. Within PMT programs, research has shown that programs based on the social learning theory are the most effective [12], of which Parent-Child Interaction Therapy (PCIT) is one [15]. PCIT is an evidence-based treatment that focuses on diminishing externalizing disruptive child behavior by strengthening parenting skills [16]. The therapy, where parents and children play together throughout a session, distinguishes itself from most other PMT programs through live coaching from the therapist, which focuses on increasing positive parenting skills [17].

PCIT has been well-researched pan culturally, with effect sizes varying between 49% and 59% [18]. Specifically in the Netherlands, PCIT has also been shown to be effective with higher effect sizes in a randomized controlled trial (RCT) comparing PCIT with a 10- to 15-session care as usual treatment (family creative therapy) available in the community mental health setting (mean 45.4, SD 3.6, for PCIT vs mean 34.0, SD 4.93 for family creative therapy; t_{23}=6.25; P<.001) [19]. Although these effect sizes indicate that PCIT is an effective treatment, this study aims to focus on the gains that can still be achieved by allowing more families to benefit from PCIT by increasing the effect sizes, accessibility, and impact of the treatment by focusing on strengthening positive parenting skills.

Worldwide, dropout rates vary between 12% and 67% [20], and specifically in the Netherlands, studies indicate that there is high attrition and that parents have a hard time grasping the different parenting skills. In that study, 52% of parents who received PCIT dropped out [19]. Attrition rates worldwide seem to be attributed to parenting stress levels and treatment barriers [20]. For instance, single parent status, problem severity of the child, and low socioeconomic status are often attributed to attrition. However, there remains some discrepancy in the literature on what factors contribute to families dropping out, although many studies have attempted to identify predictive factors [21-23]. Nonetheless, one study found that treatment completers reported significantly fewer child behavioral problems and less parental stress at follow-up than treatment dropouts [24]. This indicates that treatment should focus on making parents feel more confident in their parenting, thus potentially diminishing parenting stress and, with that, dropout rates. In further support, a study found that treatment completers showed increasing positive parenting skills and decreasing negative parenting skills from before to after treatment [21]. In addition, positive parenting skills appear to be crucial for improving the parent-child relationship [7]. A meta-analysis on PCIT showed that when meeting the skill criteria is required for completion of treatment, child externalizing behavior is significantly lower than when this is not a requirement [18]. However, when PCIT is offered in a shorter form in community samples (eg, the *standard* 12-session PCIT or the 8-session PCIT-Home), comparable effect sizes can still be yielded for a reduction in disruptive behavior [18,25]. Nonetheless, if skill criteria are met when taking the traditional PCIT protocol into account, PCIT has been shown to make impactful long-term improvements in parental warmth, responsiveness, and effectiveness [17]. In addition, studies have shown that the performance and motivation of a skill can be improved by deliberately practicing that skill [26]. Moreover, parenting programs that incorporate the opportunity to practice new skills with their children are considered more effective interventions than those that do not [27,28]. This suggests that it could be beneficial for parents to practice the skills they learn in the therapy more intensely, thereby potentially reducing dropouts and magnifying the scope of the treatment. It has previously been shown that with live coaching feedback, positive parenting skills increase rapidly, whereas negative parenting behavior decreases rapidly, especially early in the intervention. These results indicate that early interaction change in positive parenting skill acquisition is related to more positive child welfare

outcomes [29]. In addition, research indicates that a current obstacle in PCIT is that parents may have a hard time grasping parenting skills, which leads them to drop out because of the inability to fully understand and translate the parenting skills to their home setting [19]. Therefore, to bridge the gap between practicing the (Praise, Reflect, Imitate, Describe, and Enthusiasm [PRIDE]) skills in therapy and applying the skills in a home setting, this study will implement a virtual reality (VR) element. VR allows parents to practice skills regardless of whether their child is home or awake, meaning that the ability to practice skills is on demand whenever they have their smartphone device near them. Over the past years, VR has become increasingly popular within the mental health care sector, as it creates opportunities that would otherwise not be possible [30]. Thus far, research has shown that using technology in PMT programs maintains positive treatment outcomes as long as therapist contact is maintained [31]. Specifically, within PCIT, previously implemented technology augmentations, such as Pocket-PCIT, have been shown to lead to increased treatment completion rates. This indicates a promising development in using technology innovations in an attempt to tackle similar barriers to treatment engagement [28].

VR offers multiple advantages in the field of psychological research. First, a stimulus can be presented in 3 dimensions [30]. Second, a virtual environment can be manipulated and controlled to create scenarios for participants, whereas in a real-world environment, there are always variables present that cannot be controlled [32]. Third, VR technology is designed for immersion, meaning that the created virtual world becomes the real world for a moment [33]. Clearly, VR is an experience generator that opens up possibilities for creating experiences that would otherwise not be possible [33]. Thus far, in psychology and psychiatry, VR has been an effective tool in the treatment of anxiety disorders, posttraumatic stress disorder, schizophrenia, eating disorders, and substance abuse disorders [34]. It is most commonly used in exposure-based therapy and behavioral skills training [35]. Considering this study, we will focus on the use of VR for the behavioral skills training of parents. The goal is to teach certain skills to be applied in multiple environments [36]. When using VR for behavioral skills training in this study, the goal is to create an environment where the parent can additionally practice skills that they find difficult to use in the parent-child interaction. A study on the development of mindfulness skills for borderline personality disorder has shown that practicing mindfulness within a virtual environment creates the opportunity to generalize the skills to the natural context outside of therapy [37]. In addition, it has also been shown that practicing and training skills for dangerous situations, such as fire hazards in a virtual environment, are also effective [36]. These studies are precedents of how it is possible to apply VR to practice and train skills in a virtual environment. Thus, this study aims to implement VR as a low-threshold opportunity for parents to practice the skills they are taught in therapy, on their own time, within the context of their own home.

To date, no study has implemented VR to improve positive parenting skills in PCIT or in other PMT programs, although passive technological augmentations have been successful thus far [28,31]. However, considering that studies indicate that a current attrition obstacle in PCIT is that parents may have a hard time grasping the parenting skills, the addition of VR as a tool to practice skills, which can be generalized to a person's natural context, seems to be a good addition to the therapy. Nonetheless, research suggests that VR should and could, in no way, replace the clinician but rather should be integrated into the therapy to augment the intervention [38]. Therefore, the implementation of VR in PCIT creates an accessible platform for parents to further grasp positive parenting skills, thus increasing the potential for PCIT to have an impactful and lasting effect. Consequently, rather than VR being an additional layer of homework—and thus an additional life stressor—it may, in fact, alleviate parents as their ability to practice skills is essentially always *on demand*. The research group involved in this project previously tested this VR concept for PCIT with a test 360° video showing the PCIT skills [39]. This was consequently evaluated by PCIT therapists and researchers. All therapists and researchers were enthusiastic about the prospect of adding this VR element to the therapy, creating an additional opportunity for parents to practice [39]. For example, if parents are divorced and do not always have their child with them, they can practice their parenting skills nonetheless through VR. Although a double-blind RCT might be feasible in PCIT, there are significant limitations to implementing this design in clinical practice. For example, it is difficult to include a sufficiently large study population to say something meaningful about the additional VR element in clinical practice. Instead, we have chosen to use an innovative trial design, the multiple baseline single-case experimental design (SCED). This design will enable all participants to benefit from the additional VR element, which will consequently improve the power of the study compared with a traditional RCT. The design is further explained in the *Study Design* section. Therefore, the purpose of implementing PCIT-VR is to provide all parents with an easy opportunity to solidify their positive parenting skills in the comfort of their own homes.

Aims

The primary goal of this research project is to evaluate the implementation of VR in PCIT. We expect to find that PCIT-VR will ameliorate positive parenting skills, leading to faster achievement of the meeting of skill criteria. We believe that if positive parenting skills are trained more frequently by implementing the VR element, additional effects will also take place, such as achieving child-directed interaction (CDI) skill criteria sooner than when not using VR and increasing the treatment completion rate. We expect that by implementing a VR element, parents benefit from more intensive training, and VR will additionally innovatively magnify the scope of families (eg, split families with separated parents) who can benefit from PCIT. In addition, parental stress, child disruptive behavior, and analytics of VR will be secondarily measured.

As a whole, PCIT-VR is developed as an augmented version of PCIT, where the focus lies on ensuring that parents practice and learn positive parenting skills intensely. This is achieved by incorporating practicing with VR as an integral part of the therapy. The threshold for practicing skills at home using VR is low, as parents are simply able to use their smartphone

devices. PCIT-VR creates the opportunity for parents to practice and become familiar with the skills they have been taught in the therapy sessions in the comfort of their own homes. The implementation of VR functions as additional *skill training*. Providing families with PCIT-VR at an early age and early stage can potentially prevent them from needing more intensive help at a later stage and can possibly minimize the impact of child disruptive behavior, not only in the long run but also during the therapy itself.

Secondary objectives are the effects that we expect because of the overall amelioration of positive parenting skills that cause both parental stress and child disruptive behavior to diminish. Therefore, we expect that the total number of PCIT sessions will diminish and that the overall completion of treatment will increase. In addition, family dynamics and competencies will be secondarily measured, meaning that we will be able to evaluate parental compliance in the use of VR and evaluate potential risk factors for dropout. We believe that parents choosing to use VR will show higher levels of compliance as they want to use an additional tool to learn the skills. Secondary objectives also include positive VR experiences and general therapy satisfaction. Furthermore, we expect that PCIT-VR will secondarily lead to a better quality of parent-child relationships. We expect that the effects of PCIT-VR are further maintained and engrained in the long term because of the additional skill training provided by the VR scenarios.

Methods

Participants

Children (aged 2-7 years) and their parents will be referred through community channels after seeking help or support. The research will be conducted in clinical practice in the Netherlands, where families first follow a standard intake procedure (which includes an intake interview, completion of a set of questionnaires, and being referred to the right area of expertise) to establish their need for help. After this, families can be included in the study and receive PCIT-VR if the following criteria are met:

- Disruptive behavior problems of the child are a reason for referral
- Children are aged between 2 and 7 years
- Parents speak Dutch or English

A total of 15 families will be included, preferably those who finish the treatment (including all treatment phases and measurement points).

As the design is a SCED, the calculations for the number of participants are based on the What Works Clearinghouse (WWC) [40] and information gained from previous PCIT research. The WWC standards dictate that there are 5 criteria that should be acknowledged in a SCED. One of these criteria states that the minimum number of participants necessary to demonstrate an intervention effect is 3 [41]. In addition, the American Psychological Association [42] states that to display the effectiveness of an intervention, a minimum of 9 replicated single-case studies should be performed. Furthermore, attrition rates according to the standard PCIT ranged between 34% and 77% [43]. Specifically, in the Netherlands, a previous study showed a 40% attrition rate [19]. Therefore, this study will strive to include 15 families, preferably those who finish the entire trajectory to (1) adhere to a minimum of 3 participants according to WWC standards, (2) be able to state that the intervention is effective in accordance with the American Psychological Association guidelines, and (3) compensate for the potential of a 40% attrition rate.

Inclusion Criteria

Families that are referred for treatment to the clinical practice will be screened using a questionnaire for behavioral problems, the Eyberg Child Behavior Inventory (ECBI) [44] and a questionnaire about parental stress (*opvoedingsbelasting vragenlijst* [OBVL]; in Dutch) [45]. All families that are referred will be required to fill out both questionnaires on the web, where their scores are checked to see whether they meet the inclusion criteria. The clinical cutoff score for the ECBI is >131 according to US norms, meaning that all scores >131 will be included [46]. For OBVL, a T score of ≥60 is considered problematic or even clinical, thus counting as the cutoff score.

Exclusion Criteria

A potential participant who meets any of the following criteria will be excluded from participation in this study:

1. A child with severe physical impairment, such as deafness
2. A child with a mental disability (IQ<60)
3. An unsafe home situation, where home displacement is indicated
4. Child or parent with problems requiring personal health care, such as suicidality, or parents with problems with aggression regulation or addiction
5. Parents known to have severe problems with motion sickness

It should be noted that IQ will not be tested during the screening; rather, a clinical judgment will be made by the therapist or professional during intake.

Study Design

The study will use a nonconcurrent multiple baseline SCED across the 15 participants. This means that 15 individual cases will be analyzed following the same design structure. The design has been reported according to SPENT (Standard Protocol Items: Recommendations for Interventional Trials extension for N-of-1 trial protocols) guidelines [47]. SCEDs are often implemented to determine whether a causal relationship exists because of the introduction of an independent variable to the dependent variable [48]. In addition, it is frequently used when attempting to answer questions regarding the addition of a component to an intervention [49]. In terms of this study, this means that we will evaluate whether the addition of a VR element will increase positive parenting skills through multiple baseline SCEDs.

SCEDs can be used to both evaluate treatment effects for individuals and assess the efficacy of individualized treatments [48]. Although SCEDs are often compared with a case study design, there is a clear distinction: SCEDs require deliberate manipulation of an independent variable, and results from SCEDs are usually both visually and statistically analyzed

[50,51]. Another clear distinction from other designs is that SCEDs differ from experimental designs that are based on comparing groups; the manipulated variable in a SCED refers to repeated measurements of an individual who is assigned to different treatments rather than the manipulated variable being evaluated by assigning multiple individuals to different groups [50].

Strong SCEDs can be characterized by three dimensions: (1) the design is divided into phases, (2) the design contains random assignment, and (3) the design should be replicated. Incorporating these dimensions improves the internal validity of the study and minimizes the possibility of history and maturation affecting the treatment effects [50]. These dimensions are incorporated into this study (Figures 1 and 2). First, the building blocks of a phase design can be divided into a baseline phase (A) and a treatment phase (B), with each phase containing multiple measurements. This can be made more complex by, for example, adding another treatment phase (C). Second, the phase design can be randomized by having different starting points for the treatment phase. In addition, a minimum of 3 measurement points is required per phase. In this study, randomization of the length of phases is used, which is increasingly considered important to make valid inferences about results. Third, the ways in which replication can occur is 2-fold: simultaneous replication entails conducting multiple phase designs at the same time, and sequential replication entails conducting multiple SCEDs to test the generalizability of the results. When both forms of replication are used, we speak of a hybrid design, which is called a nonconcurrent multiple baseline design, where partial temporal overlap is implied [50]. To adhere to these 3 dimensions and maximize internal validity, this study will use a nonconcurrent multiple baseline design.

The strength of SCEDs, when designed with phases, randomization, and replication, is that they allow for the comparison of an individual in different phases of treatment, thus demonstrating progression while also being able to compare the treatment effects of multiple individuals at different times [50]. Analyses are conducted both visually and statistically, thus providing an aggregated overview of individual and group treatment effects. SCEDs allow for a unique perspective where clinical practice lends itself to research rather than the other way round. An individual is personally followed, and data points are manipulated to provide results rather than their treatment conditions being manipulated. Subsequently, group comparisons can be performed on the basis of an individual's own trajectory. Considering the fact that PCIT has already been widely researched, using the current design allows for an in-depth analysis of the newly implemented VR element in the treatment.

The multiple baseline SCED in this study is set up as shown in Figure 1. First, informed consent will be signed after families have received verbal and written information about the study. Second, participants will be dually randomized (by an external party) to determine their baseline period (4, 5, or 6 weeks of baseline measurements; phase A) and the addition of their VR element (VR at the start of CDI and after 3 or 6 sessions of CDI; phase B). After randomization, participants will start with phase A—the baseline period. Parents will electronically fill out the questionnaires weekly regarding child disruptive behaviors and parental stress using the ECBI and the short version of the OBVL. At the end of phase A, a pretreatment assessment will be performed. In this assessment, parents will be required to electronically fill out more questionnaires regarding both child and parental factors (Figure 1; see the *Assessment Instruments* section). In addition, the researcher will also make a video recording of the parent and child playing in 3 play situations (child-led play [CLP], parent-led play [PLP], and clean up [CU]), which will consequently be coded using the Dyadic Parent-Child Interaction Coding System (DPICS) [52]. Following this, in phase B, the intervention phase starts. Depending on their random allocation, families will start off with PCIT with or without the VR element. Once again, they will electronically fill out the ECBI and OBVL-*kort* (OBVL-K) weekly, and they will also register their homework completion and (if applicable) their VR completion sheets. During the PCIT sessions, PCIT therapists will register the parental progress weekly by coding 5 minutes of playtime with the DPICS. Once families reach CDI completion, they will move on to phase C, which is the parent-directed interaction (PDI) phase of PCIT. Measurements in phase C are identical to those in phase B. After treatment completion, a posttreatment assessment will be performed, which will be identical to the pretreatment assessment. Phase D is the follow-up assessment, which takes place 6 months after treatment completion. The assessment is also identical to the pre- and posttreatment assessments (Figure 2; 10 CDI sessions and 6 PDI sessions are used as a random example).

Figure 1. Graphical view with information per phase. AISI: Attachment Insecurity Screening Inventory; ASR: Adult Self-Report; CAPI: Child Abuse Potential Inventory; CDI: child-directed interaction; CLP: child-led play; CU: clean up; DPICS: Dyadic Parent-Child Interaction Coding System; ECBI: Eyberg Child Behavior Inventory; KJTS: Kind en Jeugd Trauma Screener; OBVL: opvoedingsbelasting vragenlijst; OBVL-K: opvoedingsbelasting vragenlijst-kort; PCIT: Parent-Child Interaction Therapy; PDI: parent-directed interaction; PLP: parent-led play; TAI: Therapy Attitude Inventory; VR: virtual reality.

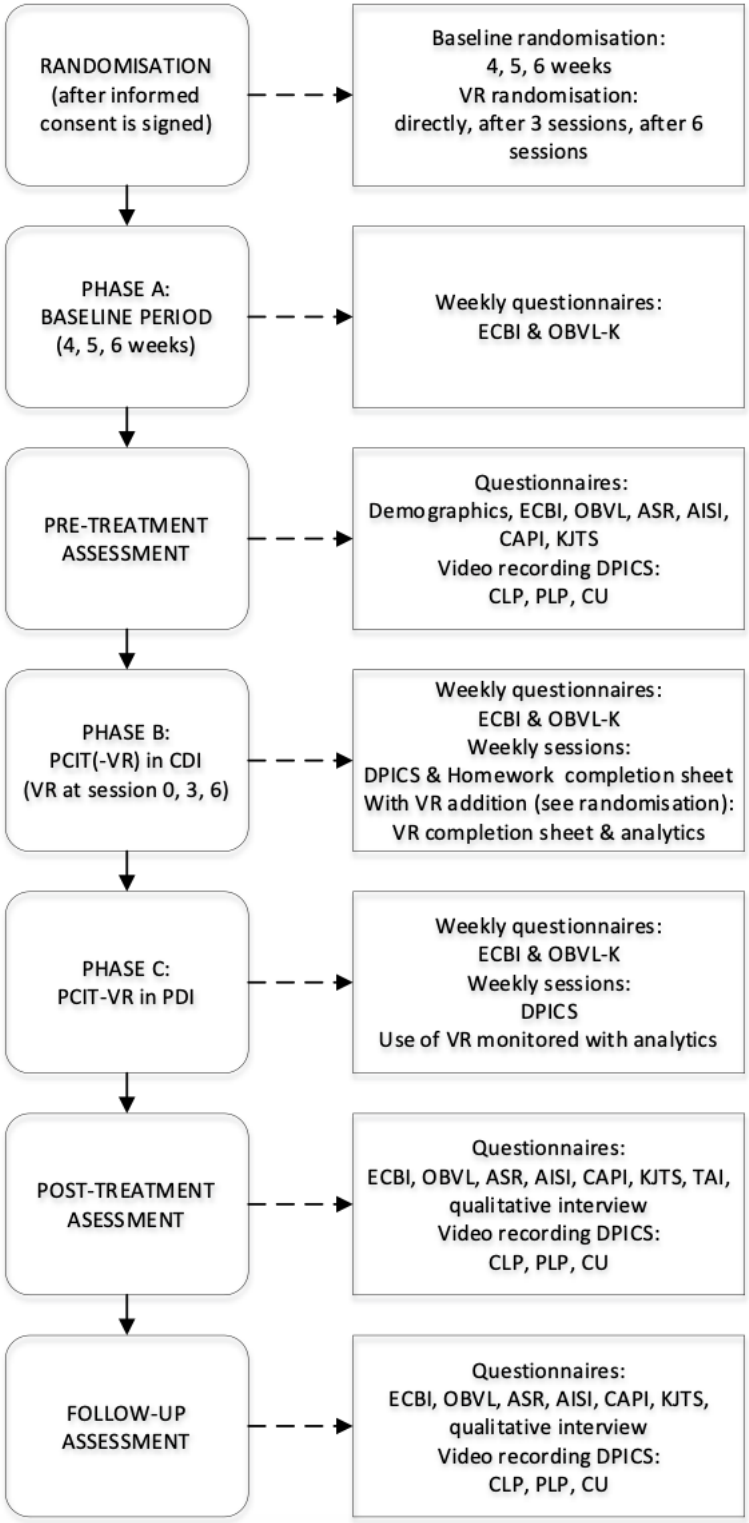
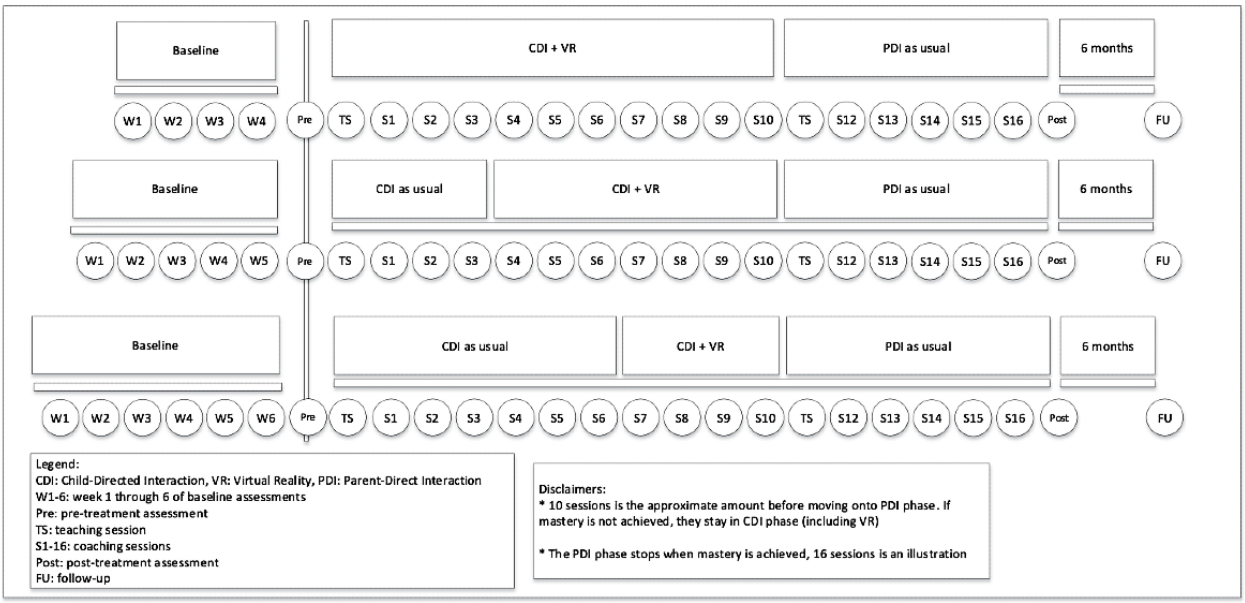


Figure 2. Three separate examples of the multiple baseline single-case experimental design in phases (using a fictitious number of allocated sessions).



Treatment

PCIT focuses on changing dysfunctional parent-child interactions in 2 phases and teaches authoritative parenting [17], which implies firm control, warmth to the parent-child relationship, and a balance between discipline and stimulating independence [53]. Therapists coach parents from behind a 1-way screen through an earpiece [17]. In the first phase of PCIT, which is the CDI phase, emphasis is placed on building up the quality of the parent-child relationship and increasing positive parenting skills. In addition, in this phase, children begin to build the ability to regulate their behavior [15]. This first phase lays the foundation for effective behavior change. In the CDI phase, parents follow their child's lead in playing and are coached on using positive parenting skills, specifically, praise, reflective statements, behavioral descriptions, imitation, and enthusiasm [17]. The number of CDI sessions is dependent on the parents meeting the skill criteria (10 behavioral descriptions; 10 reflective statements; 10 labeled praises; and <3 questions, commands, or negative verbalizations during a 5-minute observation period).

However, the CDI phase alone is typically insufficient for children with disruptive behavior to return to displaying normal behavior [54]. After meeting the CDI skill criteria, the second phase of PCIT, which is the PDI, starts. The goal of the PDI phase is to further enhance the parents' positive parenting skills to set consistent, predictable, and age-appropriate boundaries for their children [17]. In the PDI phase, parents are coached on using clear commands and how to apply consequences for compliance (praise) and noncompliance (timeout). In addition, they are taught and encouraged to keep using the positive parenting skills from the first phase. Once parents demonstrate achievement of skill criteria of both CDI and PDI skills, and their children's behaviors according to the raw score on the ECBI Intensity Scale is <114, the treatment is completed, as standard protocol dictates [17].

In October 2020, 12 therapists were trained to become PCIT therapists at a clinical treatment center in the Netherlands. They were trained by PCIT International certified trainers, thus ensuring the quality of treatment. Therapists follow PCIT protocol and have biweekly consultations with their trainers to keep track of their progress. In addition, the clinical center already had multiple PCIT therapists trained approximately 10 years ago, who also still provide PCIT to families. Both newly trained and other PCIT therapists will help collect data for this study.

VR Implementation

In the standard protocol of PCIT, parents are required to practice the skills taught throughout the sessions in *special time* at home with their children. This means that the families participating in PCIT have homework to do at home to improve weekly. This study suggests that parents also practice the skills they are taught in the sessions at home in the virtual environment that will be created for them. As such, the implementation of VR is an additional element to the standard PCIT protocol PCIT, as described previously.

There are multiple different systems within VR, one of which is a head-mounted display [30]. This study will be using 360° videos that can be played on a smartphone device placed on the head-mounted display. As a result, the person with the headset on can look around 360° from a singular point in the virtual environment, meaning that the environment does not change if the person wearing the headset decides to move. In technical terms, this is referred to as having 3 df. This option of technology was chosen as opposed to other forms of VR as it is inexpensive and easy to use through a simple (but protected) link, thus allowing people to access it from anywhere and at their own time, which increases accessibility and applicability.

The 360° video content for this study will be recorded using child actors for different scenarios. The various scenarios depict the positive parenting skills that are taught in the CDI phase (praise, behavioral description, reflective statement, and ignoring unwanted behavior), thus allowing parents to repeatedly practice these skills in the comfort of their own home. These verbalizations provide a variety of responses and depict

scenarios with commonly used toys. As there are multiple scenarios with which the parent can practice, parents are free to choose the scenarios that most suit their goal of practice.

The recorded video will be edited into fragments containing key events that call for a response from the parent by answering a multiple-choice question asked at the end of each fragment. The fragments are assembled into a therapy scenario using a web-based scenario editor in which therapy is described by a nonlinear sequence of fragments, the order of which is determined by a parent's responses. Coaching—in the way that the therapist would do in therapy sessions—is implemented by providing textual feedback to each given answer. The technology to support PCIT-VR is based on a web-based design that (1) provides a VR scenario editor, (2) functions as a server that delivers the content of a therapy scenario to the parent's headset, and (3) records performance data for future analysis. The web-based design allows the therapy scenarios to be used on any device that runs on a web browser and allows use from any location with internet access.

Assessment Instruments

The primary end point of positive parenting skills will be measured using the DPICS [52], and the added value of VR will be measured through VR assessments. Secondary end points, including the psychological functioning of the child, family dynamics and competences, and general therapy evaluation, will be measured through questionnaires and qualitative interviews. This is further explained in the following sections.

The DPICS [52] is a reliable and valid behavioral observational coding system designed to measure the quality of social interactions between parents and children. By coding open verbal and physical behaviors exhibited by both parents and children, the DPICS is able to assess the quality of the parent-child interaction as a construct. Behaviors that are coded are divided into the categories displayed in Textbox 1.

Textbox 1. Parent and child behaviors as coded in the Dyadic Parent-Child Interaction Coding System.

- Parent behaviors
  - Direct command: compliance, noncompliance, and no opportunity to comply
  - Indirect command: compliance, noncompliance, and no opportunity to comply
  - Question
  - Behavioral description
  - Reflective statement
  - Labeled praise
  - Unlabeled praise
  - Neutral talk
  - Negative talk
- Child behaviors
  - Negative talk
  - Prosocial talk
  - Question
  - Command
  - Whine
  - Yell

Coding during assessments will be done through 3 standard 5-minute play situations (CLP, PLP, and CU). Within the 5-minute observational videos, open verbal and physical behaviors will be scored on a score sheet. To progress within PCIT, parents must achieve 10-10-10 positive behaviors (10 behavioral descriptions, 10 reflective statements, and 10 labeled praises) and must display no negative leading behaviors (questions, negative talk, and commands in CDI) within the 5-minute observation time. At every assessment point during treatment, the therapist will score the parent during the 5-minute observation time with the DPICS. A video recording will be made of this, which will be used to assess the parents' progression. In addition, an independent researcher will randomly select a few of the sessions' video recordings and score the DPICS to assess the quality of the coding. Researchers will be trained beforehand to score the video recordings through DPICS and will be required to achieve an agreement rate of 80% on the scored behaviors. All observations will be transcribed verbatim to monitor interrater reliability and be subsequently double coded by an independent and reliable coder for 20% of the pretreatment, posttreatment, and follow-up treatment observations.

Further assessment instruments are divided into 4 subcategories and explained in the following sections.

VR Evaluation

VR User Analytics

Each parent will have a personal sign-in that registers their answers when using VR. Their progress will be monitored any time they log in and use a therapy scenario.

VR Completion

The parents will be required to use a VR tracking sheet, where they will fill out the number of days that they had completed the VR training. This will then be divided by the total number of days in the week, yielding a percentage of VR completion per week. Parents will be required to fill this out weekly (alongside their *special time homework completion*, which is incorporated in the standard protocol of PCIT) as soon as they receive VR.

Qualitative Interview (Parents)

Parents will evaluate the learnability and usability of their VR experience. Questions reflect on how their experience with VR was, what they believe is the added value of VR to the therapy, and whether VR helped to strengthen and comprehend parenting skills at a faster pace. They will be asked qualitative questions about their VR experience during the posttreatment and follow-up assessments. In addition, questions surrounding whether the VR simulation is compatible with their manners of speaking to their children will also be asked.

Psychological Functioning (Child)

Questionnaire Background Information

This questionnaire contains questions with regards to background information about the child and his or her family. Questions concerning sex, age, ethnicity, family composition, parental work situation, and education level are included. This questionnaire will be filled out at the pretreatment assessment. If necessary, their treatment file can be consulted for supplementary information.

Child Behavior Questionnaire: ECBI

The ECBI [44] is a questionnaire containing 36 items, which is filled out by parents and addresses child behavioral problems for children aged between 2 and 16 years. The ECBI is a part of the standard protocol of PCIT. The scale has good psychometric properties. Both the frequency of problem behavior (Intensity scale; 7-point scale from 1 [never] to 7 [always]) and the extent to which parents experience the behavior as problematic at that moment in time (Problem scale; yes or no) will be measured. Parents will complete the questionnaire at all assessment points.

Kind en Jeugd Trauma Screener

The Dutch translation of the Child and Adolescent Trauma Screen, which is the Kind en Jeugd Trauma Screener [55] screens for exposure to traumatic events and posttraumatic stress disorder symptoms. It is based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, and contains 16 items in addition to 5 dichotomous questions about how symptoms limit their daily functioning. The psychometric values of the Dutch translation are currently being researched; however, according to the English, German, and Norwegian versions of the screening questionnaire, it is valid and reliable [55]. Parents will complete this questionnaire at the pretreatment and posttreatment assessments.

Child Abuse Potential Inventory

The Child Abuse Potential Inventory [56] is a questionnaire filled out by parents, which measures the chances that parents (physically) abuse their child (aged between 0 and 18 years). All 34 items include a statement with which parents could either *agree* or *disagree*. The psychometric properties of the Dutch translation have been shown to be reliable and valid [57]. This study will use the short version. Parents will fill out this questionnaire at the pretreatment and posttreatment assessments.

Family Dynamics and Competences

Dutch Parenting Stress Questionnaire: OBVL

The OBVL [45] is a Dutch questionnaire with 34 questions that address five aspects of parenting stress: problems in the parent-child relationship, problems in parenting, depressed moods, role restriction, and health complaints. The total score on parenting burden can be calculated. The OBVL has high reliability, and norms have been measured for different age groups, indicating that its psychometric properties are good. Parents will complete this questionnaire during pre- and posttreatment and follow-up assessments.

Dutch Parenting Stress Questionnaire, Shortened Version: OBVL-K

The OBVL-K [45] is a shortened version of the OBVL. It comprises 10 questions that together provide a total score on the burden of parenting. This questionnaire has high reliability, and norms have been measured for different age groups, indicating that its psychometric properties are good. Parents will complete this questionnaire weekly to obtain a general overview of their parental burden throughout the process.

Adult Self-report

The Adult Self-Report [58] is a self-report measure of competencies and emotional and behavioral problems for adults and is based on the Diagnostic and Statistical Manual of Mental Disorders. The questionnaire is split into 2 sections, one concerning competencies and work and the second concerning emotional and behavioral problems. The English version has been shown to be reliable and has good validity. The psychometric properties of the Dutch version are yet to be evaluated. The parents will complete this self-report during pre- and posttreatment assessments.

Attachment Insecurity Screening Inventory

The Attachment Insecurity Screening Inventory (AISI) [59] is a questionnaire that measures attachment problems. The questionnaire contains 20 items that together form total attachment but are divided into three subcategories: avoidant, ambivalent/resistant, and disorganized attachment. The AISI 2-5 was found to be valid and reliable according to recent research [59]. The AISI 6-12 is practically identical to the AISI 2-5 but has not been tested for validity and reliability. Nonetheless, studies have shown that the AISI is a promising

instrument for measuring attachment insecurity in young children [59]. The AISI will be filled out by parents during the pre- and posttreatment assessments.

Therapy Evaluation

Therapy Attitude Inventory

The Therapy Attitude Inventory [60] is a 10-item scale that evaluates parental satisfaction with the treatment. This questionnaire will be filled out once by the parents at the end of the treatment. Although information regarding the reliability and validity of the Dutch translation of the TAI is missing, the original version has shown adequate psychometric properties [61].

Qualitative Interview (Parents)

A qualitative interview after treatment and follow-up assessments will allow parents to share their experiences with regard to the new form of PCIT-VR and the extent to which this therapy strengthened their competences and made them see their own abilities.

Qualitative Interview (Therapists)

Therapists will also be asked about their experiences and vision of the effectiveness of PCIT and their vision of the added value of VR to the therapy at the end of the data collection period. They will be asked what factors contribute to effectiveness, including factors such as their relationship with parents or specific characteristics. Through this interview, the different benefits and obstacles of PCIT-VR can be brought to light through the eye of the therapist.

Statistical Analysis

Data analysis will take place in consultation with a statistics expert from the Clinical Research Unit department of the Amsterdam University Medical Center (UMC). Data analysis will include the following:

1. Primarily, the added value of VR to PCIT will be evaluated through analyses.
2. SCED analyses will be conducted with the Shiny app.
3. Repeated measures analyses will be conducted.
4. Graphical analyses will be conducted to render the change over time.

Qualitative information from the interviews will be summarized into a complete picture of the experiences of both parents and therapists. This will include their experiences with PCIT-VR, the VR component in particular, and how the therapy helped them gain insight into strengthening their competencies. All qualitative information will be analyzed using structured qualitative interview software, for which we will also seek consultation with an expert.

Confidentiality of Data

The data for this study will be collected by researchers from the Department of Child and Adolescent Psychiatry at the Amsterdam UMC. The Clinical Research Unit of the Amsterdam UMC provides support for the data analysis of this study. All data will be stored in coded form by assigning personal numbers to each family and registering all information using that number. This ensures that only authorized people can trace which file belongs to which family. All study results will be published anonymously.

Ethics Approval

This study was approved by the medical ethics committee of the Academic Medical Center of Amsterdam, Netherlands (2020_143). Informed consent for participation in the study will be obtained; among other permissions, parents will also provide permission for video recording of their child. The way informed consent will be obtained for the study was approved by the medical ethics committee of the Academic Medical Center of Amsterdam, the Netherlands (2020_143).

Results

As of February 2021, 6 families have been enrolled in the study at the time of submission. Data collection is projected to be completed in 2023. Both quantitative and qualitative results are planned to be published in peer-reviewed journals, as well as being presented at national and international conferences. The study is registered at the medical ethics committee of the Academic Medical Center of Amsterdam, the Netherlands (2020_143/NL74210.018.20) and the Netherlands Trial Register NL9580.

Discussion

Principal Findings

This study is the first to implement a VR element that functions as additional *skill training* to magnify the scope of PCIT through practice. Similar to standard PCIT, the intervention is centered around parent-child play sessions, where parents receive live feedback and support from a therapist. The additional VR element provides parents with the opportunity to practice positive parenting skills in the comfort of their own homes without their child present while still receiving feedback. This allows them to further engrain the skills alongside the therapy sessions and special time. Therefore, we expect that the implementation of VR will lead to faster achievement of meeting the skill criteria. Furthermore, this study expects that parental stress, child disruptive behavior, dropout rates, and the number of necessary therapy sessions will diminish as a secondary effect of the additional VR element.

Currently, the technology behind the VR element is being developed in parallel with the study, meaning that the development of VR is fluid. This is an asset as it means that the application can be adapted if any technical problems arise. A potential problem that could be encountered and should be resolved as soon as possible is the functioning of the web-based VR application on different smartphones. The application, the videos, and the technology that underlies this must be designed in such a way that it is supported by all types of smartphones and their software versions. To find the right fit for smartphones, testing must be performed on multiple devices before offering them to parents. To minimize the potential obstacles and rather use them as learning points, close contact will be kept with both technical support and parents. Parental feedback will be processed as soon as possible by the technical support, and

adaptations will be made where and when necessary. Fortunately, SCEDs lend themselves well to this flexibility, as each individual trajectory has different phases (baseline and treatment phase), thus enabling comparison between phases and even between measurement points. This means that the VR obstacles faced by one family may differ from those of another family. Therefore, this study offers an opportunity to flexibly implement VR and register individual obstacles as they occur, both qualitatively and quantitatively.

The implementation of VR later on in CDI sessions could potentially limit its effect on improving positive parenting skills, as the rate of skill growth from session to session usually gradually declines as families get closer to meeting skill criteria. Nonetheless, the strength of SCEDs designed with phases, randomization, and the opportunity to replicate means that it allows for the comparison of an individual in different phases of treatment. Thus, it allows us to follow progression while also being able to compare the treatment effects of multiple individuals at different times. As analyses are conducted both visually and statistically, a clear overview can be provided for both individual and group treatment effects. This means that both individual and group outcomes can indicate whether the timing of VR implementation affects the effect on acquired positive parenting skills. However, SCEDs also have some potential limitations. For example, there is a risk of type I errors because of the potential violation of distributional assumptions and the presence of serial dependencies. In addition, it is possible that there is an unexpected data trend because of maturation effects (eg, gradual bettering of VR analytics because of habituation to scenarios). With the right statistical support, these pitfalls can potentially be mitigated, which is something the research group intends to do.

Conclusions

The clinical practice in which the study is conducted lends itself well to the research on VR implementation in this study. This means that every family that participates already provides enough data to be able to say something meaningful about the treatment and VR. Overall, this study can be seen as a stepping stone to implementing VR on a larger scale within PCIT to ultimately magnify the scope of the treatment through additional skill training.

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Authors' Contributions

ICAS conceptualized and designed the final study protocol. MEA was a major reviewer, and RGB, AP, and RJLL reviewed the final study protocol. ICAS wrote the manuscript. All authors (ICAS, MEA, RGB, AP, and RJLL) read, edited, and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AISI: Attachment Insecurity Screening Inventory
CDI: child-directed interaction
CLP: child-led play
CU: clean up
DPICS: Dyadic Parent-Child Interaction Coding System
ECBI: Eyberg Child Behavior Inventory
OBVL: opvoedingsbelasting vragenlijst
OBVL-K: opvoedingsbelasting vragenlijst-kort
PCIT: Parent-Child Interaction Therapy
PDI: parent-directed interaction
PLP: parent-led play
PMT: parent management training
PRIDE: Praise, Reflect, Imitate, Describe, and Enthusiasm
RCT: randomized controlled trial
SCED: single-case experimental design
SPENT: Standard Protocol Items: Recommendations for Interventional Trials extension for N-of-1 trial protocols
TAI: Therapy Attitude Inventory
UMC: University Medical Center
VR: virtual reality
WWC: What Works Clearinghouse

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Protocol

Peer Mentoring Program for Informal Caregivers of Homebound Individuals With Advanced Parkinson Disease (Share the Care): Protocol for a Single-Center, Crossover Pilot Study

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Abstract

Background: Homebound individuals with advanced Parkinson disease (PD) require intensive caregiving, the majority of which is provided by informal, family caregivers. PD caregiver strain is an independent risk factor for institutionalization. There are currently no effective interventions to support advanced PD caregivers. Studies in other neurologic disorders, however, have demonstrated the potential for peer mentoring interventions to improve caregiver outcomes. In the context of an ongoing trial of interdisciplinary home visits, we designed and piloted a nested trial of caregiver peer mentoring for informal caregivers of individuals with advanced PD.

Objective: The aim of this study was to test the feasibility of peer mentoring for caregivers of homebound individuals with advanced PD and to evaluate its effects on anxiety, depression, and caregiver strain.

Methods: This was a single-center, 16-week pilot study of caregiver peer mentoring nested within a year-long controlled trial of interdisciplinary home visits. We recruited 34 experienced former or current family caregivers who completed structured mentor training. Caregivers enrolled in the larger interdisciplinary home visit trial consented to receive 16 weeks of weekly, one-to-one peer mentoring calls with a trained peer mentor. Weekly calls were guided by a curriculum on advanced PD management and caregiver support. Fidelity to and satisfaction with the intervention were gathered via biweekly study diaries. Anxiety, depression, and caregiver strain were measured pre- and postmentoring intervention at home visits 2 and 3.

Results: Enrollment and peer-mentor training began in 2018, and 65 caregivers enrolled in the overarching trial. The majority of mentors and mentees were White, female spouses or partners of individuals with PD; mentors had a mean of 8.7 (SD 6.4) years of caregiving experience, and 33 mentors were matched with at least 1 mentee.

Conclusions: This is the first study of caregiver peer mentoring in PD and may establish an adaptable and sustainable model for disease-specific caregiver interventions in PD and other neurodegenerative diseases.

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International Registered Report Identifier (IRRID): DERR1-10.2196/34750

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KEYWORDS

Parkinson disease; carer; caregiving; care partner; peer mentor; peer support; depression; anxiety; caregiver strain; volunteer; intervention

Introduction

Background

Parkinson disease (PD) affects over 1 million individuals in the United States, with a projected 77% increase in prevalence by 2030 [1,2]. Although PD is classified as a movement disorder, the nonmotor and neuropsychiatric symptoms and complications frequently overshadow mobility concerns as the disease progresses [3-6]. Indeed, the leading causes of hospitalization in PD are falls, urinary incontinence or infection, dehydration, and neuropsychiatric changes—such as dementia, hallucinations, delusions, agitation, and depression. Many of these hospitalization triggers are preventable or treatable at home if recognized and addressed promptly, which requires a knowledgeable and observant caregiver [7]. Once hospitalized or institutionalized, people with PD suffer excessive iatrogenic morbidity and mortality.

A critical, understudied, and independent risk factor in both hospitalization and institutionalization in PD is caregiver strain [8-10]. Ample evidence links PD caregiver strain to acute health care utilization for the patient and to adverse caregiver health consequences [3,11-13]. Furthermore, caregiver strain is higher in PD than in many other neurodegenerative conditions, likely due to the complexity and synergistic effects of the motor, nonmotor, and cognitive symptoms [13-16]. However, few interventions have targeted caregiver strain in this population despite significant work highlighting unmet needs for education, prognostic counseling, and support for PD caregivers [17-19]. The lack of evidence-based caregiver interventions is not limited to PD. In 2020, the National Institute on Aging published a systematic review on behavioral interventions for individuals with dementia and their caregivers, concluding that while an intensive, multicomponent intervention may improve caregiver depression at 6 months, the majority of other interventions and care models demonstrated minimal positive effect [20]. Many caregiver interventions also rely on costly measures performed by the medical team that are both time- and effort-intensive [21].

In prior work, we developed interdisciplinary home visits for homebound individuals and their caregivers affected by advanced PD and related disorders [22]. Home visits appeared to disentangle the expected parallel declines in quality of life and disease severity, such that while mobility worsened over 1 year, quality of life did not follow a similar trajectory [23]. Despite this promising effect seen in patients, among those patients who had a caregiver who participated in longitudinal assessments, caregiver strain worsened over 1 year. We identified key challenges faced by these caregivers from our own cohort and from published studies, including an unmet need for education and social connection among caregivers with similar experiences [24-27].

An intriguing approach to supporting individuals with chronic disease pairs a current caregiver with an experienced past caregiver who is trained as a peer mentor. The mentor offers one-to-one support of the current caregiver (mentee) by providing guidance, resources, and a relationship for problem solving and encouragement [28]. The structure and outcome measures of these studies have varied widely, yet some have improved caregiver strain and confidence [29-31]. Early studies matched Alzheimer disease and Alzheimer disease–related dementias (AD/ADRD) caregivers with peer mentors to bolster coping skills and social support [30-32]. Qualitative data showed benefits for caregivers and mentors although quantitative results were equivocal, likely due to variable implementation [30,33]. Subsequent successful models of peer mentoring have been tested in individuals with end-stage renal disease and advanced cancer, and among older adults to encourage physical activity [34-38]. However, there is a knowledge gap regarding the content, logistics, and implementation of peer mentorship. In anticipation of the proof-of-concept study of peer mentoring among advanced PD caregivers described here, we surveyed a convenience sample of past and current advanced PD caregivers regarding their interest in this kind of program. Over 83% (15/18) expressed interest in being a peer mentor, 50% (9/18) reported prior use and comfort with video chat apps to facilitate mentoring calls, and among those without prior experience, 78% (14/18) indicated willingness to try the technology. We also reviewed notes from 29 PD caregiver support group sessions to identify themes for a PD-specific peer mentoring program.

Objectives

In response to the success of our home visit pilot program, we designed a larger, controlled trial of interdisciplinary home visits for homebound patient-caregiver dyads with advanced PD versus usual care [39]. In recognition of the dearth of existing interventions, our own data demonstrating progression of strain despite home visits, and interest among caregivers for their own caregiver-directed intervention, we developed a caregiver peer mentoring program entitled Share the Care, nested within the larger year-long home visit trial. Our specific aim for Share the Care was to compare the effects of home visits plus caregiver peer mentoring versus home visits alone on caregiver mood in a single-cohort, crossover design. We hypothesized that caregivers participating in both home visits and nested peer mentoring would have decreased depression and anxiety after 16 weeks of a structured peer mentoring intervention as measured by the change in the Hospital Anxiety and Depression Scale (HADS) [40]. Here, we describe the study design and implementation of Share the Care. We describe the mentor training process and curriculum as well as the structure of peer mentoring and present the baseline characteristics of caregiver peer mentors and mentees, respectively. We also outline the challenges identified in the recruitment and retention

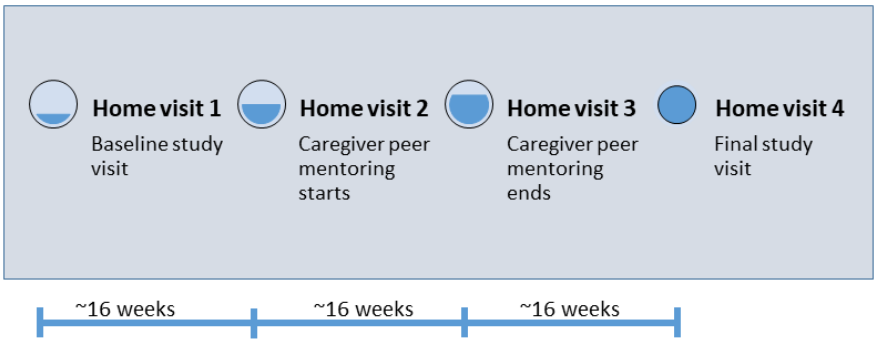
of both mentors and mentees that will shape future iterations of this model of caregiver support.

Methods

Study Setting, Design, and Recruitment

This is a pragmatic, single-center, 16-week, single-cohort, crossover study of peer mentoring, nested in a controlled trial of interdisciplinary home visits for individuals with advanced PD and their caregivers (IN-HOME-PD). The full details of IN-HOME-PD have been published previously [39]. Briefly, IN-HOME-PD patient and caregiver dyads received 4 home protocol-driven home visits from a nurse and a social worker, each enhanced by a real-time telehealth connection with a movement disorders specialist over the course of approximately one year. The study described herein occurred between the second and third home visits for each dyad as illustrated in Figure 1.

Figure 1. Study design.



The recruitment target for IN-HOME-PD was 65 patient-caregiver dyads, with recruitment beginning in the first quarter of 2018 and ending in the fourth quarter of 2019. Patient-caregiver dyads were recruited from the Rush University Medical Center in Chicago, Illinois, and the caregiver member of each dyad served as the mentee in the nested study described here.

Peer mentor recruitment took place between the second quarter of 2018 and the first quarter of 2019. Recruitment was multipronged in order to identify caregivers with both the experience, time, and temperament necessary to serve as a peer mentor. First, we searched the electronic medical record (EMR) and a voluntary registry of current and former patients maintained at Rush's Parkinson's Disease and Movement Disorders Program, filtering for patients with a PD diagnosis, seen within 3 years, and with a record of death. These criteria were selected to ensure that the respective caregiver would be familiar with advanced PD, close to having received care at Rush, yet not actively caring for their loved one such that mentoring would be onerous or exacerbate bereavement. All potential mentors identified through the EMR or database were discussed with the previously treating neurologist prior to the study team contacting them. Second, we approached neurologists at Rush's Parkinson's Disease and Movement Disorders Program for provider-generated recommendations of caregivers, including those who were still actively caring for their loved ones but might have had the capacity for mentoring. Third, the Rush Philanthropy department provided a list of individuals who had expressed gratitude for their loved ones' care within the Rush Program and who might have been amenable to participation. Finally, the principal investigator (JEF) presented Share the Care to leadership at CurePSP, a foundation dedicated to individuals with atypical parkinsonian conditions, including progressive supranuclear palsy, corticobasal syndrome, multiple system atrophy, and Lewy body dementia. As these diseases share many similarities with advanced PD, experienced caregivers from the CurePSP support group leader network were also eligible to participate as peer mentors and were referred directly by CurePSP leadership.

Mentor and Mentee Eligibility Criteria

Peer mentors were recruited to provide emotional support to up to 2 mentees, sequentially, during the mentor program. All mentors were current or former caregivers who had at least 2 years of informal caregiving experience for an individual with PD or an atypical parkinsonian condition. Mentors were at least 30 years old and primarily English-speaking. They were required to attend a 1-time, in-person mentor training session at Rush University and commit to up to 2, sequential, 16-week blocks of peer mentoring (see Textbox 1 for a complete list of inclusion and exclusion criteria).

Textbox 1. Share the Care mentor and mentee eligibility criteria.

Mentor inclusion criteria

- Aged ≥30 years
- >2 years of informal caregiving experience for an individual with Parkinson disease (PD) or a related disorder: dementia with Lewy bodies, progressive supranuclear palsy, multiple system atrophy, and corticobasal syndrome
- Previously participated in a caregiver support group for PD or related disorder, participated in a PD educational or outreach event, or given permission to be contacted for research
- English as primary language
- Able to attend a 5-hour mentor training session at Rush University
- Willing to commit to two, 16-week blocks of peer mentoring either in person, by telephone, or by videoconference for a minimum of 30 minutes per week
- Working telephone number

Mentee inclusion criteria

- Aged ≥30 years
- Caregiver in the Interdisciplinary Home Visits for Parkinson Disease Patient trial
- Cohabitating or spending ≥20 hours per week engaged in care-related tasks for a homebound individual with advanced Parkinson disease
- English as primary language
- Capacity to consent
- Working telephone number

Mentor and mentee exclusion criteria

- Terminal illness with a life expectancy of <12 months by self-report
- Exhibiting symptoms of a severe psychiatric disorder

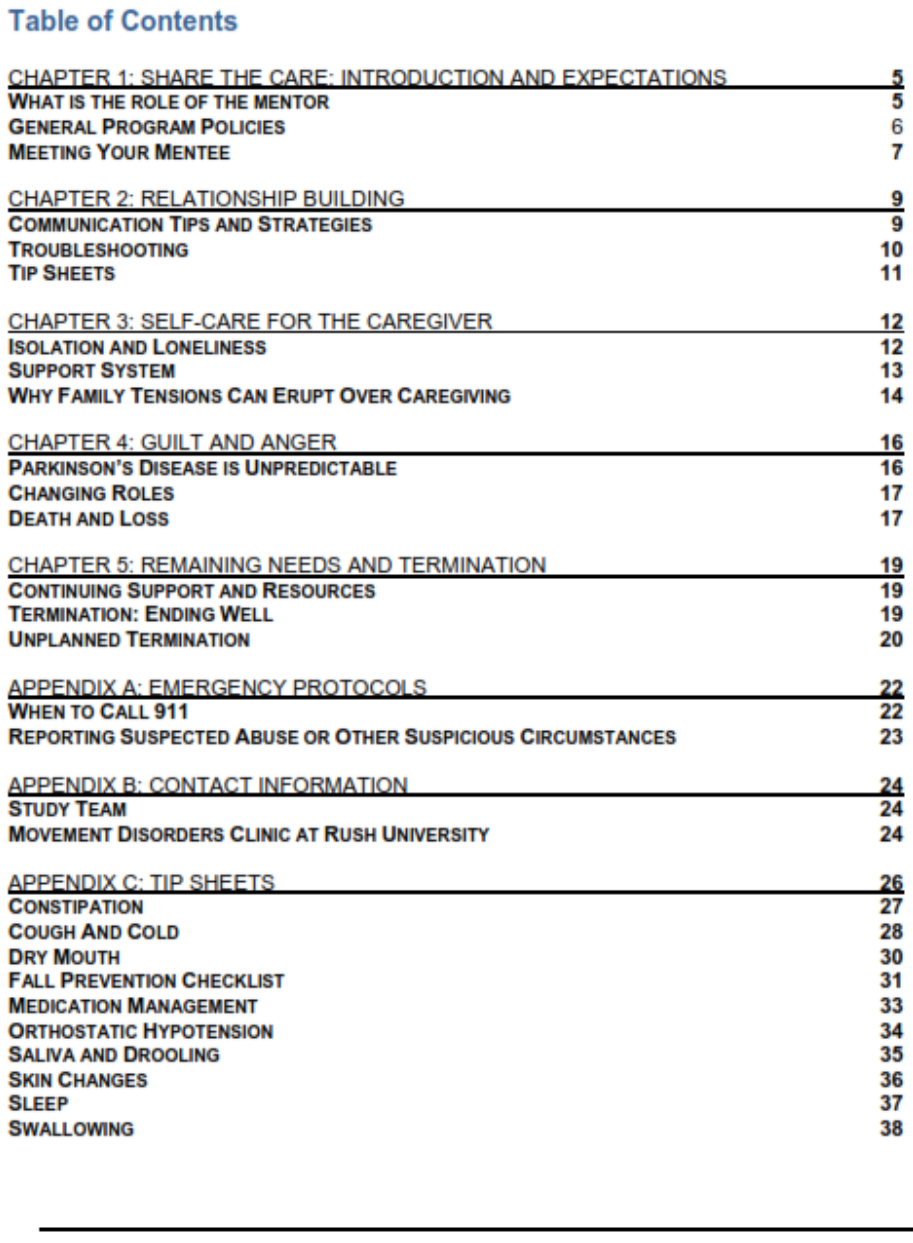
All mentees were unpaid, informal caregivers for a homebound individual with advanced PD who had consented to and enrolled in the IN-HOME-PD study, the details of which have been described in detail elsewhere [39]. Mentees either cohabitated with or spent an average of 20 or more hours per week engaged in care-related tasks for a homebound, community-dwelling individual with advanced PD. If mentees were informal caregivers who subsequently obtained compensation for less than 1 quarter of their caregiving hours via local or state resources, these caregivers could participate. Mentees who self-reported a life expectancy of less than 1 year or who were exhibiting symptoms of a severe psychiatric disorder were excluded from participation. Mentees were matched with a mentor at the second of 4 quarterly home visits. All mentees completed the mentor program during the 16-week period between the second and third home visits.

Intervention

Mentor Curriculum

To provide a formal structure for the mentor program, we created the “Share the Care” mentoring handbook (table of contents shown in Figure 2; entire handbook in Multimedia Appendix 1). This handbook draws on topics identified as being important to individuals with advanced PD and their loved ones [41]. The handbook suggests key discussion topics for mentoring calls and guides mentors through the logistics, skills, and topics relevant to mentoring relationships.

Figure 2. Handbook table of contents.



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Mentor Training

Potential mentors were provided with detailed information about the study and were screened for eligibility by phone by a member of the study team (ECK). Eligible individuals who elected to participate were scheduled to attend 1 of 3 five-hour, in-person training sessions at Rush University Medical Center. At the training session, mentors completed the informed consent process individually prior to any study activities taking place. After consent was obtained, mentors completed demographic questionnaires and baseline assessments of anxiety, depression, and caregiver self-efficacy (see Outcomes Measure below). Because all enrolled mentors had varying backgrounds and experiences with patients with PD and related disorders, a movement disorders specialist (JF) gave a detailed presentation on the rationale for the study, including prior home visit studies and research on PD caregivers. Next, lectures continued on the stages, common motor and nonmotor symptoms, and the management of sudden and gradual changes in advanced PD. In this way, all mentors were provided with a primer on advanced PD in order to relate to their mentees' challenges, even if their own loved ones had not experienced certain symptoms. The study team's social worker (JL) discussed the role of a mentor and mentorship skills, including being present, empathic listening, setting boundaries, maintaining confidentiality of all discussions, and brainstorming solutions to potentially challenging scenarios (eg, unrealistic mentee expectations of the mentor, unequal commitment to the study between the pairs, health crises, and life changes). The study team provided mentors with and reviewed the Share the Care handbook, offering suggestions on how to use it to support mentoring calls. All mentors were given the option of using a data plan–enabled iPad (Apple) provided by the study team to communicate with their mentees by videoconference. Mentors who elected to communicate this way were trained to use an iPad by a study team member (SPH, ECK, or JL). Mentors who

preferred to use their own devices for videoconferences or who preferred to use telephone calls were permitted to do so.

Peer Mentoring

Given the rolling enrollment in the broader IN-HOME-PD study, each mentor was matched with 1-2 mentees over the course of the year following mentor training. To the extent possible, mentors and mentees were matched on the basis of similar age, sex, and relationship to a loved one with PD (eg, adult child, spouse or partner) although extensive matching criteria have not improved outcomes in prior peer mentoring work in AD/ADRD [28,42]. Each mentoring relationship lasted 16 weeks. Mentors were asked to speak with their mentee for 30 minutes weekly, either by phone, videoconference, or in person. Mentors were given their mentees' contact information and asked to initiate mentoring. The mentors could refer to the "Share the Care" handbook to guide the weekly discussions but were free to focus on topics of concern to their mentees as they arose. Following the 16-week relationship with their first mentee, mentors had a break of 0-16 weeks, depending on their own scheduling needs and how many mentees were eligible to start mentoring at any given time. If available and necessary, mentors were then paired with a second mentee with whom they completed a second 16-week relationship.

Mentors and mentees maintained simple study diaries documenting when each conversation took place, how the pair connected (phone, videoconference, or in person), the length of the conversation, general topics discussed, whether they found the discussion useful, and any issues that occurred. To ensure fidelity, individual team members checked in with each participant at weeks 2, 4, 8, 12, and 16, when participants relayed the information in their study diaries to the study team member.

Finally, mentors were invited to participate in optional quarterly conference calls with other mentors and a member of the study team (JL). During these calls, mentors were invited to share their experiences and successes in their mentoring relationships, and to discuss any issues they had encountered. These calls provided opportunities for peers and the study team to validate the mentors' successes and challenges, and for the study team to proactively address any concerns.

Retention Efforts

Mentors received quarterly e-newsletters about the study and annual holiday cards to promote engagement and study retention. Upon study completion, the team sent each mentor a personalized thank you note and a certificate of appreciation. Mentee retention efforts included encouragement at quarterly home visits and interim follow-up calls regarding clinical care and psychosocial needs. In the event of a patient death, the study team sent a handwritten condolence card to the mentee and notified the respective mentor.

Outcome Measures

Table 1 lists the instruments used to collect data from mentees and mentors, respectively, at each relevant time point during the study. For mentors, all baseline data were collected at the mentor training session. For mentees, demographic data were collected at the first home visit. Outcome measures were collected at home visit 1 (baseline), 16 weeks later at home visit 2 or week 0 of mentoring (prementoring baseline), 16 weeks later at home visit 3 (postmentoring), and finally 16 weeks later at home visit 4 (longitudinal follow-up).

Table 1. Assessments completed by mentees and peer mentors.

Domains	Instruments	Study visit							
		HV[a] 1	HV 2	Wk 2	Wk[b] 4	Wk 8	Wk 12	HV 3 Wk 16	HV 4
Mentee									
Demographics	Demographics questionnaire	✓							
Anxiety and depression	Hospital Anxiety and Depression Scale	✓	✓					✓	✓
Self-efficacy	Caregiver Self-Efficacy Scale	✓	✓					✓	✓
Caregiver strain	Multidimensional Caregiver Strain Index	✓	✓					✓	✓
Study fidelity	Study diary – frequency, date, duration, topic of mentoring call			✓	✓	✓	✓	✓	
Satisfaction with program	Client Satisfaction Inventory-Short Form							✓	
Peer mentor									
Demographics	Demographics questionnaire	✓							N/A[c]
Anxiety and depression	Hospital Anxiety and Depression Scale	✓						✓	N/A
Self-efficacy	Caregiver Self-Efficacy Scale	✓						✓	N/A
Study fidelity	Study diary: frequency, date, duration, topic of mentoring call			✓	✓	✓	✓	✓	N/A
Satisfaction with program	Client Satisfaction Inventory Short Form							✓	N/A

[a]HV: home visit.

[b]Wk: Week of Share the Care mentoring program.

[c]N/A: not applicable.

Mentee and Mentor Demographic Characteristics

Participants indicated their age, sex, race, ethnicity, highest level of education, primary language, marital status, relationship to care recipient with PD (or in the case of mentors, relationship to care recipient with PD or a related disorder), and years spent caregiving for that individual. As mentors were eligible to participate whether they were still actively caregiving or not, mentors alone were asked whether their care recipient was still alive. If living, the mentor was asked to disclose the care recipient's living situation (eg, own home, assisted living facility, subacute or skilled nursing facility). If deceased, the mentor was asked to disclose how long ago the care recipient had died.

Implementation: Fidelity and Satisfaction Measures

To examine fidelity to the Share the Care intervention, mentors and mentees were asked to complete study diaries to document when each conversation took place, the format (eg, phone call, videoconference), duration in minutes, topics discussed, whether or not they found the discussion useful, and any issues that occurred. Both mentors and mentees received check-in phone calls from study team members (ECK and JL) at weeks 2, 4, 8, 12, and 16. During these phone calls, mentors and mentees were asked to provide the information recorded in their study diaries; in the event that the participant had not documented an entry, the study team member asked them to provide a verbal response to each question. Finally, both mentors and mentees completed the Client Satisfaction Inventory Short Form (CSI-SF) [43] assessment at home visit 3 or postmentoring to measure their satisfaction with Share the Care.

Primary and Secondary Outcome Measures

Among mentees and mentors, we assessed mental health using the HADS, a validated measure with individual anxiety and depression domains, for which scores >8 on either domain indicate probable symptoms [40]. Given the use of the HADS in prior peer mentoring interventions, this was selected as our primary outcome to facilitate sample size calculations and comparison with historical data [33]. As secondary outcomes, we administered the 9-item Caregiver Self-Efficacy Scale to both mentors and mentees at their respective baselines and at the end of the 16 weeks of mentoring [44]. This scale measures one's belief in one's ability to succeed in specific situations or accomplish a task, with domain subscores for symptom management and community support service use self-efficacy. Participants were instructed to complete this instrument according to how they felt on the day of administration; in the case of mentors who were no longer actively caregiving, they were prompted to answer as if they were still actively caregiving. As an additional secondary outcome, mentees completed the Multidimensional Caregiver Strain Index (MCSI) at home visits 1 and 2, and again after 16 weeks of mentoring. The MCSI is an 18-item assessment, validated in PD caregiver populations,

spanning 6 dimensions of caregiver strain, with a score range of 0 (no strain) to 72 (worst possible strain) [3,45]. MCSI dimensions include physical, financial, and interpersonal strain; social and time constraints; and demanding behaviors on the part of the care recipient.

Statistical Analyses

Sample Size Calculations

Sixty-five patient-caregiver dyads were enrolled in the larger IN-HOME-PD study based on a power calculation for the overarching study's primary outcome of patient quality of life. All 65 caregivers consented to participate in the peer mentoring program as mentees. Assuming a mean HADS of 12 (SD 7) based on a trial of peer mentoring for caregivers of patients with dementia, 4 clusters of 15 caregivers each, a coefficient of variation of 0.3, a 2-sided significance level of 0.05, and power of 0.8, we concluded that 65 caregivers would afford the ability to detect a difference of 3.5 points in the HADS [30,33]. We assumed that each mentor would be paired with up to 2 sequential mentees, such that 34 mentors were recruited, assuming 10% attrition during the year-long mentor program.

Analytic Plan

We will use an intention-to-treat approach for all analyses, with per-protocol sensitivity analyses. We will describe the demographics, baseline depression and anxiety (HADS subscales), and self-efficacy of mentees and mentors, and caregiver strain (MCSI) of mentees only. To assess the implementation of the intervention, we will present the frequency and duration of mentoring calls. In the event of discrepant reports between the paired mentor and mentee, the number of calls or duration in minutes will be averaged. We will report the satisfaction of both mentors and mentees with the intervention using the CSI-SF and the percentage of calls rated as useful. Assessing for normality and using parametric or nonparametric tests as appropriate, we will compare within-subject change in anxiety, depression, and self-efficacy, respectively, over the 16 weeks of mentoring. We will then assess within-subject change of mentees and mentors each over the entire study for each of the primary and secondary outcomes to assess for crossover effects from home visits only (home visit 1 to home visit 2), Share the Care only (home visit 2 to home Visit 3), and the combined interventions (home visit 1 to home visit 4). We will construct linear regression models with change in depression, anxiety, strain, and self-efficacy, respectively, as the dependent variables, and a 16-week time frame (visits prementoring, visits with mentoring, visits alone postmentoring) or full study duration as the primary independent variable. We will adjust for potential confounders: caregiver demographics, mentoring visit frequency and duration, and risk factors for caregiver strain (motor fluctuations, falls, cognitive impairment, hallucinations, and poor quality of life) [3,8]. We will explore the heterogeneity of treatment effects using within-cluster comparisons of exposed (mentored) and unexposed (home visits only) time [46].

Data Management

Data were collected on paper case report forms and entered into a secure, regulation-compliant electronic database [47,48], with quarterly audits for fidelity. Data will be exported to Stata 15 (StataCorp) for analysis.

Ethical Considerations

Approval was obtained from Rush University Medical Center's Institutional Review Board on October 24, 2017 (number 17080209-IRB01). Two separate informed consent documents were developed for peer mentors and caregiver or mentees, respectively, including the details of their involvement in the study based on the 2 unique roles. All participants in the study provided written informed consent.

Results

Trial Status

Study recruitment began in February 2018 for mentees and May 2018 for mentors. We enrolled 65 mentees and 34 mentors into the program, and all mentors completed 1 of 3 in-person training sessions held by the study team in August 2018, November 2018, and February 2019. Following this, 33 mentors were matched with at least 1 mentee and all mentoring relationships concluded in November 2020. Due to pandemic-related delays, data cleaning and analysis were conducted throughout 2021, with dissemination of results anticipated to occur in the second half of 2022 via peer-reviewed publications and ClinicalTrials.gov.

Baseline Characteristics of Mentors and Mentees

Baseline characteristics of mentors and mentees are shown in Tables 2 and 3. The majority of mentors (20/34, 59%) and mentees (51/65, 78%) were female. The mean age of mentors was 63.6 (SD 13.3) years and that for mentees was 66.1 (SD 6.4) years. Most participants identified as White (mentors: 26/34, 76%; mentees: 46/65, 71%) and were the spouse or partner of the person with PD for whom they were caring (mentors: 22/34, 65%; mentees: 39/63, 62%). Mentors enrolled in the program were all experienced caregivers, with an average of 8.7 (SD 6.4) years of caregiving experience. Only 4 mentors were still actively caring for their care recipient, while the remaining mentors' care recipients were deceased.

Table 2. Baseline characteristics of caregiver peer mentors.

Characteristic	Outcome (N=34)
Age (years), mean (SD)	63.6 (13.3)
Female, n (%)	20 (59)
Race, n (%)	
White	26 (76)
Asian	5 (15)
Hispanic	1 (3)
More than 1 race	1 (3)
Unknown/declined to answer	1 (3)
Care recipients' diagnosis, n (%)	
Parkinson disease without dementia	10 (29)
Parkinson disease with dementia/Lewy body dementia	5 (15)
Multiple system atrophy	2 (6)
Progressive supranuclear palsy	16 (47)
Corticobasal syndrome	1 (3)
Relationship to care recipient, n (%)	
Spouse/partner/significant other	22 (65)
Adult child	11 (32)
Family friend or neighbor	1 (3)
Caregiving time (years), mean (SD)[a]	8.7 (6.4)
Care recipient alive, n (%)	4 (12)
Time since care recipient death (years), n (%)[b]	
Less than 1 year	5 (17)
1-2 years	9 (30)
2-5 years	14 (47)
More than 10 years	2 (7)

[a]n=33.

[b]n=30; the remaining 4 mentors were still actively caregiving.

Table 3. Baseline characteristics of mentees.

Characteristic	Outcome (N=65)
Age (years), mean (SD)[a]	66.1 (11.5)
Female, n (%)	51 (78)
Race, n (%)	
Caucasian	46 (71)
African American/Black	11 (17)
Asian	6 (9)
Unknown/declined to answer	2 (3)
Hispanic, White, or declined to identify race, n (%)	4 (6)
Care recipients' diagnosis, n (%)	
Parkinson disease without dementia	40 (62)
Parkinson disease with dementia/Lewy body dementia	25 (39)
Relationship to care recipient, n (%)[b]	
Spouse/partner/significant other	39 (62)
Adult child	19 (30)
Other family member	3 (5)
Family friend or neighbor	4 (6)
Part-time home health aide	1 (2)

[a]n=63.

[b]Mentors selected all relationships that applied.

Discussion

This is the first structured study of peer mentoring for caregivers of homebound individuals with advanced PD, and to our knowledge, the first study of caregiver peer mentoring in PD in general. We expect that this novel pilot intervention will be met with high fidelity and satisfaction, given the unmet needs of this population of caregivers and the opportunity to share experiences with a knowledgeable peer. Caregiving in PD is associated with higher direct and indirect caregiving costs, greater strain and burden, and larger ramifications for caregiver health outcomes compared with caregivers of individuals with AD/ADRD [13,15,49,50]. A recent cross-sectional study confirmed that many PD caregivers rely on peers for advice [51], and a pilot study demonstrated the feasibility and high satisfaction of a caregiver tele-support group [52]. However, many behavioral interventions in PD have targeted the patient-caregiver dyad [53] or have been patient-focused with caregiver assessments as secondary outcomes [54]. For interventions aimed at improving caregiver outcomes, it may be necessary to limit activities to caregivers only or to provide opportunities for caregivers to participate apart from their care recipient. In the presence of the care recipient, social desirability bias and an understandable wish to preserve the care recipient's privacy and dignity may limit the caregiver's participation. Although Share the Care was nested within a broader patient-facing intervention, a particular strength is that the peer mentoring activities were entirely limited to the caregivers and their trained mentors, creating a safe and confidential space for discussing caregiving challenges, successes, and resources.

Several limitations arose in this pilot study. First, identifying and recruiting experienced mentors proved more difficult than had been anticipated. When individuals with PD have been institutionalized or have died, their caregivers may no longer be connected to the care recipients' health care providers or social networks. This can pose a challenge both to recruitment from caregiver-facing sources, such as support groups or educational symposia, but also from provider referrals. Providers may be primed to recall caregivers of patients seen more recently rather than patients who have died or who have become estranged from routine care. We also found many individuals known to be deceased by their treating provider who were not marked accordingly in the EMR and adapted recruitment strategies to include provider reviews and clear descriptions of the time commitment required of mentors, as many had their own comorbidities or were still actively caregiving, which precluded the time necessary for training and mentoring. Due to the challenges recruiting PD caregivers as mentors, we expanded our recruitment to include mentors who had cared for loved ones with atypical parkinsonian disorders. We aimed to address the heterogeneity of mentors' caregiving experiences through mentor training, acknowledging both that symptoms of advanced PD and the atypical disorders overlap significantly, and that even within PD, symptoms can vary from person to person. Nonetheless, the variability of mentors' experiences may bias their interactions and limit generalizability. Furthermore, Share the Care was nested within the broader

home visit study. Many caregivers consented to the entire study with the primary draw being home visits. For some caregivers, Share the Care might have been of lesser interest.

In future work, a peer mentoring intervention distinct from direct patient care may attract caregivers who recognize the need for additional support and who are explicitly interested in a peer mentoring relationship. Additionally, future directions include expanding eligibility to caregivers of nonhomebound individuals and offering virtual mentor training sessions to reach a larger and potentially national pool of mentors. Future iterations would be well-informed to incorporate behavior change theories and proven behavior change techniques to address frequently encountered complications in advanced PD and in caregiving for this population. Further studies are also needed to compare the efficacy and acceptability of individual mentoring with more traditional support groups or other group interventions.

Analysis of the Share the Care peer mentoring pilot study and the overarching home visit study is ongoing. We anticipate that the results and qualitative feedback from participants will inform the development of much-needed support interventions in families living with advanced PD and subsequently, across the disease spectrum. If successful, subsequent stand-alone programs will be developed and tested for caregivers of individuals with PD, atypical parkinsonian disorders, and AD/ADRD. Such a program could potentially impact the lives of millions of caregivers by providing information and resources while fostering connections with informed, experienced, and sympathetic peers. If successful, this model may also promote the transition of mentees into eventual peer mentors, building a pipeline of support for future caregivers. Given the rising prevalence of PD and the increasing reliance on family caregivers, effective and sustainable interventions are urgently needed to fill this critical gap.

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Data Availability

The deidentified data sets generated and analyzed during this trial will be made available from the corresponding author upon reasonable request.

Authors' Contributions

JEF, DAH, and JC conceived the program, secured grant funding, and wrote the protocol; JL and JEF drafted the "Share the Care" handbook; ECK recruited all mentors and mentees; JEF, JL, SPH, and ECK led mentor training sessions; JL, ECK, SPH, and EM collected study data. BO provided sample size calculations and statistical analyses. FA, ECK, ML, and JEF drafted the manuscript. JW, DAH, and JC provided ongoing critical review. All authors reviewed and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Handbook distributed to caregivers.
[PDF File (Adobe PDF File), 275 KB - resprot_v11i5e34750_app1.pdf]

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Abbreviations

AD/ADRD: Alzheimer disease and Alzheimer disease–related dementias
CSI-SF: Client Satisfaction Inventory Short Form
EMR: electronic medical record
HADS: Hospital Anxiety and Depression Scale
IN-HOME-PD: Interdisciplinary Home Visits for Individuals with Advanced PD
MCSI: Multidimensional Caregiver Strain Index
PD: Parkinson disease

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Protocol

A Web-Based Public Health Intervention for Addressing Vaccine Misinformation: Protocol for Analyzing Learner Engagement and Impacts on the Hesitancy to Vaccinate

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Abstract

Background: A barrier to successful COVID-19 vaccine campaigns is the ongoing misinformation pandemic, or infodemic, which is contributing to vaccine hesitancy. Web-based population health interventions have been shown to impact health behaviors positively. For web-based interventions to be successful, they must use effective learning design strategies that seek to address known issues with learner engagement and retention. To know if an intervention successfully addresses vaccine hesitancy, there must be some embedded measure for comparing learners preintervention and postintervention.

Objective: This protocol aims to describe a study on the effectiveness of a web-based population health intervention that is designed to address vaccine misinformation and hesitancy. The study will examine learner analytics to understand what aspects of the learning design for the intervention were effective and implement a validated instrument—the Adult Vaccine Hesitancy Scale—to measure if any changes in vaccine hesitancy were observed preintervention and postintervention.

Methods: We developed a fully web-based population health intervention to help learners identify misinformation concerning COVID-19 and share the science behind vaccinations. Intervention development involves using a design-based research approach to output more effective interventions in which data can be analyzed to improve future health interventions. The study will use a quasi-experimental design in which a pre-post survey will be provided and compared statistically. Learning analytics will also be generated based on the engagement and retention data collected through the intervention to understand what aspects of our learning design are effective.

Results: The web-based intervention was released to the public in September 2021, and data collection is ongoing. No external marketing or advertising has been done to market the course, making our current population of 486 participants our pilot study population. An analysis of this initial population will enable the revision of the intervention, which will then be marketed to a broader audience. Study outcomes are expected to be published by August 2022. We anticipate the release of the revised intervention by May 2022.

Conclusions: Disseminating accurate information to the public during pandemic situations is vital to contributing to positive health outcomes, such as those among people getting vaccinated. Web-based interventions are valuable, as they can reach people anytime and anywhere. However, web-based interventions must use sound learning design to help incentivize engagement and motivate learners to learn and must provide a means of evaluating the intervention to determine its impact. Our study will examine both the learning design and the effectiveness of the intervention by using the analytics collected within the intervention and a statistical analysis of a validated instrument to determine if learners had a change in vaccine hesitancy as a result of what they learned.

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KEYWORDS

public health; population health; education; gamification; COVID-19; vaccination; misinformation; infodemic; vaccine hesitancy; web-based health; web-based intervention; learning design; dissemination

Introduction

Background

In 2020, the world began to face the challenges of COVID-19. As the year shifted to 2021, a new hope emerged in the form of a vaccine, and with that came concerns from the public over the role that vaccines play in public health and the safety of vaccines, leading to the emergence of an infodemic of misinformation on the internet and social media [1]. Recent studies have suggested that social media platforms act as a medium for health misinformation to spread more easily than scientific knowledge [2,3]. The definition of *health misinformation* is "a health-related claim that is based on anecdotal evidence, false, or misleading owing to the lack of existing scientific knowledge" [4,5]. *Health misinformation* is a term that considers false information that does not aim at harming others but has had an apparent role in the recent pandemic. These concerns and others have contributed to a phenomenon known as *vaccine hesitancy*, which is defined as a "delay in acceptance or refusal of vaccination despite the availability of vaccination services" [6]. Health communication has been shown to play an essential role in combating behaviors related to vaccine hesitancy [6,7]. When health communication is poor, it can undermine individuals' confidence in a vaccine, leading to vaccine hesitancy. Effective health communication strategies are proactive and ensure the accuracy and reliability of information by using means that are easily accessible to the public. Factors that influence the success of health communication strategies include providing mechanisms through which individuals can receive information, communicate their needs, connect with others, and mobilize community engagement [6]. One way of using health communication is through public health education interventions. Public health education interventions successfully raise awareness about public health concerns and change behaviors and perspectives toward various diseases [8]. For example, education interventions have played a vital role in the prevention and control of communicable diseases, such as SARS (severe acute respiratory syndrome) [9] and MERS (Middle East respiratory syndrome) [10], by aiding in improving learner anxiety, depression, and fear [9]. It stands to reason that public health education may also positively impact vaccine hesitancy related to COVID-19 vaccines.

Health education interventions aim to improve the access to and delivery of information to address social determinants of health and empower behavior change [11]. There are many different approaches to developing interventions, including individual methods, group methods, and mass media methods [12]. Each of these methods has its own benefits that aid its effectiveness and its own barriers [13]. Web-based health education interventions are useful in reaching a broad audience, as they can overcome physical barriers, enabling education to be accessible anywhere and anytime. However, web-based interventions come with their challenges. As demonstrated by research in massive open online courses (MOOCs), completion rates for web-based interventions vary greatly, and such interventions tend to have high attrition rates [14]. A lack of learner motivation and a lack of interactivity have been reported as contributing factors [15]. Paying attention to the design of learning is a way of engaging and motivating learners to achieve learning objectives [14]. Learning design is the process of designing education by giving thoughtful consideration to content and activities for describing, understanding, supporting, and guiding the practices and processes of learning [16]. Given that enrollment in web-based interventions is only expected to rise, learning designs must implement effective strategies to promote learner engagement, motivation, and learning outcomes.

The Institute for Excellence in Health Professions Education (ieHPE) at the Mohammed Bin Rashid University of Medicine and Health Sciences (MBRU) has a history of implementing effective and successful web-based population health education interventions. For example, our *Community Immunity Ambassador* series, which was designed to engage the public in understanding, preventing, and coping with the COVID-19 pandemic, went viral, with over 1 million learners engaging with these initiatives. Over time, the ieHPE has systematized its way of designing and developing initiatives to incorporate strategies for educating learners and motivating and empowering them to share information with others. The ieHPE uses an iterative approach to design and develop interventions that involves using small, multidisciplinary teams consisting of educational experts, subject matter experts (SMEs), and digital content creators.

Objective

The objective of this protocol is to describe the development of a web-based educational intervention that is designed to address vaccine misinformation and the proposed analysis of data to understand if there was any impact on learners' hesitancy to vaccinate. The intervention will use a pre-post test design involving the use of a validated instrument called the *Adult Vaccine Hesitancy Scale* (aVHS) [17] to measure changes in vaccine hesitancy. Each learner will complete the aVHS at the beginning and end of the intervention. In addition, the analytics collected about how users interacted with the intervention will also be analyzed to understand how to make the intervention more effective.

Our research questions include the following:

1. What kinds of learner engagement did we observe in the course (ie, use patterns, levels of engagement, and completion rates)?
2. What changes are observed in a participant's vaccine hesitancy status as a result of the learning, as determined by a pre-post validated survey tool (aVHS)?
3. What kind of improvements or alterations are recommended to the course based on our observations?

Methods

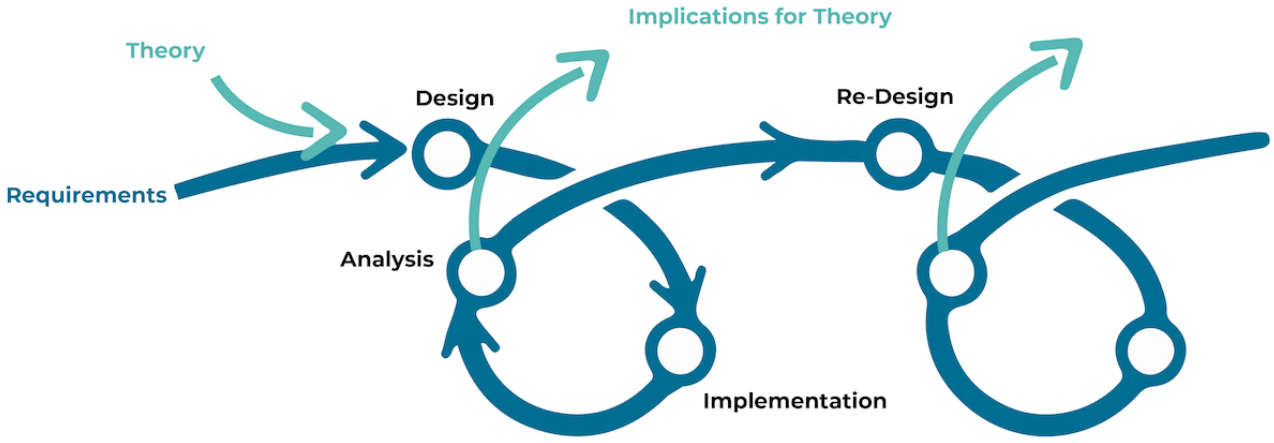
The methods for our study are described below in 2 parts. The first part describes the methodology behind the design and development of the web-based intervention, and the second part describes the aVHS instrument [17] and analysis of the data that we will collect.

Design and Development of the Web-Based Intervention

Our web-based intervention is publicly available at no cost on our web-based course platform—MBRU Learn. The intervention was developed to educate learners about (1) how to mitigate becoming infected with SARS-CoV-2, (2) how to spot and prevent the sharing of misinformation and disinformation related to COVID-19 and vaccines, and (3) the science behind vaccinations and their impact on public health. The intervention uses learning design principles to motivate learners to complete the intervention and empower them to share their new knowledge and achievements. The Center for Learning and Teaching methodology for intervention design includes keeping initial project teams small and agile to allow for quicker turnaround times. Several prototypes were created iteratively among this small team, which were sent to a larger pool of SMEs and testers for review and feedback. The three core members of this project team consisted of an SME, an educational expert, and a digital content developer. In addition, our SME was a physician with expertise in public health and vaccination outreach.

The Center for Learning and Teaching strategy draws on principles from design-based research (DBR), in which successive iterations of design, analysis, implementation, and reflection are used to ensure the practical application and success of the intervention (Figure 1) [18,19]. DBR has been described as a practical approach to "bringing about transformation through the design and use of solutions to real problems" [20]. The guiding principles of DBR include (1) inquiry into a problem of practice to generate usable knowledge to inform intervention and theory, (2) close collaboration between researchers and practitioners in the design and development of interventions (ie, new tools, instructional materials, etc), and (3) the use of iterative design cycles for the design and continuous improvement of interventions [18,20,21]. Using DBR rather than an instructional design model, such as the Analyze, Design, Develop, Implement, and Evaluate approach [22] or the successive approximations model [23], helps to better ensure that development and research stay closely linked, creating an opportunity to contribute to both theory and practice.

Figure 1. Design-based research process, as adapted from Fraefel [20].



Description of Phases

The requirements phase consisted of a project meeting for discussing the intervention. Our requirements phase determined the learning objectives, audience, and platform for the intervention, as well as the time requirements for the intervention's release and the data we will analyze to determine if we are successful. The learning objectives are detailed as follows: at the end of the course, the learner should be able to (1) describe the negative impact that misinformation has on the pandemic, (2) evaluate information to avoid misinformation traps, (3) apply strategies to reduce the risk of contracting and spreading COVID-19, and (4) recognize the science behind vaccinations and how they work to protect public health.

The platform for dissemination will be the MBRU's public-facing, web-based platform, which is called *MBRU Learn*. The platform offers rapid course development services, simple registration and marketing methods, and the ability to collect various types of learner engagement and assessment information.

After the requirements phase, our team entered the design phase, in which we ideated on a theme for the course and the learning design strategies. We determined that we would use gamification strategies in both the learning design and the graphic

development process. The gamification techniques in the intervention include using graphics and media to simulate a fun, video game–like experience (Figure 2) and using elements such as progress tracking through the collection of objects (Figure 3) and demonstrating growth by moving up in levels toward the final level, in which the learner slays the "big boss" (Figure 4). The intervention concludes with the awarding of a certificate and an invitation to a social media campaign, in which the learner can share achievements with others by using a unified hashtag.

Figure 2. Screenshot from the educational intervention—participants' avatar in its final state.

Figure 3. Screenshot from the educational intervention—collection of objects.

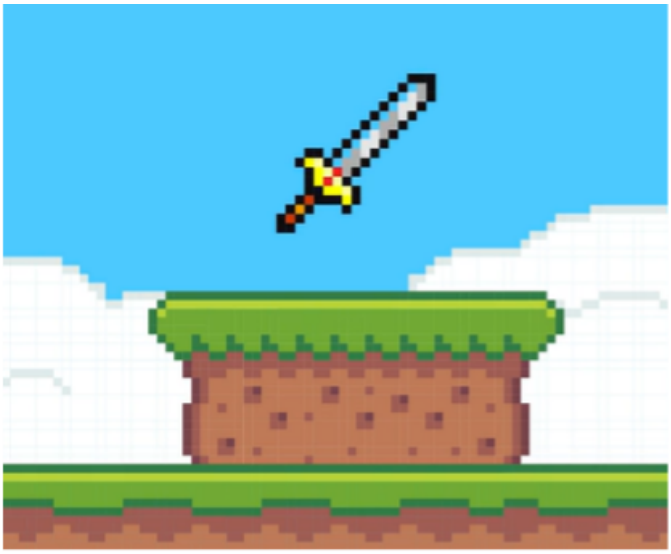
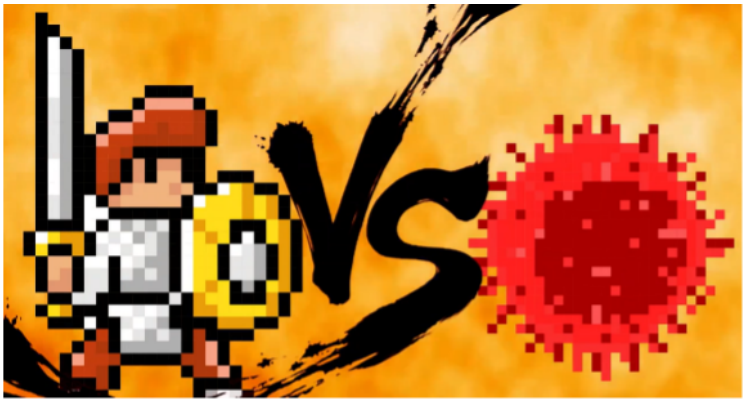


Figure 4. Screenshot from the educational intervention—final "big boss" challenge.



We iterated through several storyboards and prototypes during the design phase, and each iteration grew in in terms of the complexity of the content and graphics until a fully developed beta intervention was achieved and sent to additional SMEs for feedback. Feedback from the SMEs was then incorporated into the next iteration to reach the version that was implemented on MBRU Learn. The final, implemented version of the intervention consists of the following three chapters: (1) *Understanding and counteracting misinformation*, (2) *COVID-19 transmission and prevention*, and (3) *The science*

of vaccinations. A combination of media is used in each chapter, including videos, motion graphics, audio, and text. A knowledge check is performed at the end of each chapter. Learners have unlimited attempts to pass the knowledge check and cannot proceed until a grade of 100% is achieved. Once the knowledge check is passed, the learners are presented with an animated video to acknowledge their avatar's new rank (Figure 5).

As part of the implementation phase, we decided not to market or promote the intervention on the internet actively, limiting the number of participants and enabling us to pilot the intervention. The data collected from this first pilot population will be considered for the first iteration of the analysis phase, which will form the basis for answering the research questions described in this protocol.

Figure 5. Screenshot from the educational intervention—ranks and equipment for each stage.

Measuring Change in Vaccine Hesitancy

Various scales have been developed to measure vaccine hesitancy among parents or health care workers [17]. The World Health Organization Strategic Advisory Group on Experts Working Group on Vaccine Hesitancy developed a 10-item Vaccine Hesitancy Scale that is widely used in different countries and settings [24]. The Vaccine Hesitancy Scale has been modified to the aVHS and has been adapted and validated in English and Chinese [17]. The aVHS is a 10-item scale with a 5-point Likert scale ranging from "Strongly disagree" to "Strongly agree." The Likert scale items have scores ranging from 10 to 50, where 50 represents the highest degree of vaccine hesitancy, and 10 represents the lowest degree of vaccine hesitancy. Further, 7 items on the scale will be reverse coded, so that the highest scores reflect the highest degree of vaccine hesitancy [17]. A cutoff score of 24 will be used to dichotomize the outcomes into the "vaccine hesitant" and "not vaccine hesitant" categories. All scores and cutoffs will be adopted by following the methodology of the research team developing the scale [17].

Data Collection

The study will use a quasi-experimental design (ie, a pre-post test using the aVHS) to understand if any changes have occurred in learners' hesitancy to vaccinate. The aVHS is embedded in the intervention, and it will be completed by the learner before and after the intervention, with results being stored on a secure server. In addition, analytics data are collected automatically by MBRU Learn, which records how learners engage with the intervention, including the amount of time they spent using the intervention.

All data will be collected within MBRU Learn, which is securely hosted locally at the MBRU. Therefore, only the research team will have access to the data. The data collection instruments will include the aVHS, and analytics of interactions with the intervention and sociodemographic data, including participants' age range, country of residence, gender, and vaccination status, will be collected. Participants will also be asked about how they heard about the course.

Recruitment

MBRU Learn is a web-based space that hosts all of our publicly available web-based interventions, enabling participants to

locate and enroll in interventions quickly and free of charge. We will not actively recruit participants to the intervention for the study described in this protocol. As such, participants will include those who find the course by coming to the MBRU Learn platform either through previous experience with the platform or by word of mouth. After the revised intervention is released, we will actively market the course to the public through social media and email marketing.

Ethics Approval

The study was approved by the university's institutional review board in October 2021 (submission number: MBRU IRB-2021-68).

Data Analysis

Sample Size

An a priori sample size calculation was conducted by using G*power (Universität Düsseldorf). A total sample size of 343 has a power of 95% (1 − β error probability) and an α error probability of 5% for detecting an effect size of 0.2 (20%).

Data Analysis Plan

Our data analysis plan describes how we will answer the research questions related to how learners engage with the course and any vaccine hesitancy changes. Learner engagement will be quantitatively analyzed by using the analytics data collected in MBRU Learn. Our analysis will focus on learner engagement and retention analytics—the two most common measurements that are used to understand and improve web-based interventions [25]. Learner engagement will be determined by analyzing analytics such as the time spent on lessons and activities, engagement with digital resources, the number of attempts for quizzes and assessments, the number of times content was viewed, and the amount of time spent overall on the intervention. Retention will be determined by understanding the overall completion rates. Recommendations for revisions to the course will be based on the analysis results. Next, we will use these analysis results and existing literature to make determinations about how the intervention can be made more effective, after which we will enter another iteration in the DBR process to output an improved intervention that will be heavily marketed on social media and to our existing database of over 1 million learners.

Impacts on vaccine hesitancy will be analyzed based on the pre-post aVHS test scores. Statistical analysis software will be used to analyze the data set, and a complete case analysis approach will be adopted. Data will be tested for normality visually, by using histograms, and statistically, by using the Shapiro-Wilk test. The significance level cutoff will be set at $P<.05$, and exact P values will be reported. Continuous variables will be further categorized after data visualization to avoid having groups with sparse data. Means, medians, IQRs, and SDs will be used to describe continuous variables. For categorical or nonnormally distributed variables, a Wilcoxon signed rank test will be used. Frequency distributions, percentages, and chi-square tests will be used to describe binary and categorical variables and identify any significant differences.

The correlation between vaccine hesitancy scores and the vaccination statuses reported by participants will also be explored. aVHS scores will be summed (range: 10-50), and hesitancy will be determined according to the tool's design (scores of 10-24 will be categorized as "not hesitant," and scores of 25-50 will be categorized as "hesitant"). The primary outcome results will be presented as proportions of vaccine-hesitant individuals with the corresponding 95% CIs. The vaccine hesitancy statuses will be stratified by participants' gender, age range, and country of residence. A pre-post comparison of the responses to the aVHS will be conducted by using a Wilcoxon signed rank test. ANOVA analyses and regression models will be constructed to evaluate the potential confounding effect that arises from variations in the sociodemographic factors of participants. The significance level cutoff will be set at $P<.05$, and exact P values will be reported.

Results

The study described in this protocol is part of a larger research project titled "Addressing Vaccine Hesitancy through Targeted and Personalized Mobile Educational Interventions for Different Populations in the Eastern Mediterranean region." The university's institutional review board approved the study in October 2021 (submission number: MBRU IRB-2021-68). Data collection began in September 2021, and it is ongoing. This protocol describes the study, which will use data collected from September 2021 to January 2022, as outlined in our institutional review board approval. Once the analysis is complete and another round of DBR has been conducted, the improved intervention will be released, and promotion activities will commence to recruit participants. The study outcomes are expected to be published by August 2022. We anticipate the release of the revised intervention by May 2022. In addition, any work resulting from our study will be disseminated nationally and internationally through submission to academic journals and international conferences.

Discussion

Study Implications

Population health education plays a crucial role in the prevention and control of diseases. Methods of population health education are varied and can consist of simple awareness campaigns, pamphlets, advice from health professionals, or web-based education interventions [9]. The factors to consider when designing health education to address pandemics include addressing the fear and stigma that members of the public might feel [26], which can contribute to dangerous behaviors, such as denying infection and delaying health care uptake [9]. The World Health Organization developed guidelines to address the issue of social stigma, and one of the main components is "spreading the facts," which explains that stigma is enhanced with insufficient knowledge about a disease's mode of transmission, treatment, and prevention. This could be rectified via the collection and dissemination of sound and accurate information [27]. It was found that anxiety levels significantly decreased after adequate health education [9] and awareness improved. Hence, the learning design of our intervention

includes digital literacy skills for identifying misinformation and wellness techniques that can help address issues of anxiety related to COVID-19 and vaccines. Our health education intervention aims at improving knowledge and perceptions and empowering individuals by increasing self-efficacy among the general population. The web-based course is publicly available, and it will be continuously improved and updated to address areas of concern regarding COVID-19. It serves as a reliable resource for individuals who have questions and concerns that need to be addressed in a creative and interactive way.

As discussed previously, for web-based interventions to succeed in changing behaviors, considerations of learning design and motivation strategies must be undertaken. However, due to the limitations within our platform and a lack of available resources, we cannot use typical learning and motivation strategies, such as establishing a social presence on discussion forums or through group work, to motivate learners to finish our courses [28,29]. Hence, in our learning design, we use strategies such as reflection, which helps connect learners to their prior experiences and establish relevance; use the provision of immediate feedback on knowledge checks to support competence; create an engaging experience through variations in learning activities and digital content; and use gamification principles, such as a progression strategy, whereby the intervention is told through a story in which the learner is the hero [14,30,31].

In their systematic review of papers on using gamification for MOOCs, de Freitas and da Silva [25] found that studies that used gamification principles reported greater participation from learners, as reflected by the time spent on MOOC platforms, the number of learners completing end-of-course evaluations, and the number of tasks and lessons completed [25]. Gamification in education involves applying game design elements to improve learner engagement and motivation [32]. Gamification is commonly linked with self-determination theory, which looks at the concept of motivation, focusing on individuals' intrinsic (internal) and extrinsic (external) motivation [33]. The characteristics of intrinsic motivation include curiosity and interest in learning new things [34]. It has been recommended that interventions that use gamification strategies be carefully designed to balance considerations for intrinsic and extrinsic motivation [34,35]. Given that our educational intervention is entirely voluntary and is not part of a formal curriculum, it can be safely assumed that our learners are intrinsically motivated. As such, our educational intervention uses extrinsic motivation techniques to stimulate our learners toward completing the entirety of the intervention and sharing their accomplishments via social media.

Limitations

The limitations in the study are related to the current intervention and the dissemination of the intervention thus far. The current intervention is only available in English, limiting our participant population. The intervention also only exists on the internet, limiting our participant population to those with digital literacy and internet access. Additionally, no personal or sociodemographic data will be collected from the participants until the end of the course, limiting these data to those from participants who achieve 100% completion. We have also chosen not to publicly disseminate the course, limiting the participants to those who are likely already followers of other community health courses in MBRU Learn or those who advocate for our courses already. This can skew the completion statistics, as these participants may be highly motivated to participate in the intervention. However, analytic observations of highly motivated participants are valuable measures, as they may help us identify larger errors more easily in our design. Despite this population limitation, we believe that its impact on our understanding of learner engagement will be limited and that the analysis of vaccine hesitancy status via the aVHS will not experience the same bias. Current and subsequent iterations of the intervention will only be available on MBRU Learn, which might only reach a limited demographic. However, our future direction is to use Google ads to promote the intervention to a larger population. The absence of an adequate control group is also another limitation in the study's ability to assess the impact of the intervention on vaccine hesitancy, which will otherwise be measured via a pre-post scale. Adopting a pre-post survey (quasi-experimental design) is very common, especially in studies on educational interventions. The assumption is that the impact of the knowledge gained will be identified based on the changes in the test scores. One of the known limitations of this design is the use of a pretest, which potentially informs participants about the matter of interest and allows them to score better on a posttest rather than acquire adequate general knowledge on the subject of interest [36]. This has been controlled for in our study by blinding the participants to the scores of the scale and the interpretation of those scores. Also, participants act as their own controls in the study design. This controls for other potential confounding factors.

Conclusions

Our study will explore the use of a web-based educational intervention that is designed to address vaccine misinformation and observe any changes in learners' hesitancy to vaccinate. The results of the study will contribute to using evidence-based practices to better understand how to develop public health interventions that contribute to positive health behavior changes, such as the willingness to vaccinate and the identification of public health misinformation. Any work resulting from this project will be disseminated nationally and internationally through submission to academic journals and international conferences.

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Conflicts of Interest

None declared.

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Abbreviations

aVHS: Adult Vaccine Hesitancy Scale
DBR: design-based research
ieHPE: Institute for Excellence in Health Professions Education
MBRU: Mohammed Bin Rashid University of Medicine and Health Sciences
MERS: Middle East respiratory syndrome
MOOCs: massive open online courses
SARS: severe acute respiratory syndrome
SME: subject matter experts

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Protocol

Tailoring and Evaluating an Intervention to Support Self-management After Stroke: Protocol for a Multi-case, Mixed Methods Comparison Study

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Abstract

Background: Self-management programs are recognized as a valuable approach to supporting people with long-term conditions, such as stroke, in managing their daily lives. Bridges Self-Management (Bridges) focuses on how practitioners interact and support patients' confidence, skills, and knowledge, and it is an example of a complex intervention. Bridges has been developed and used across multiple health care pathways in the United Kingdom and is theoretically informed by social cognition theory and self-efficacy principles. Evidence shows that self-management programs based on the construct of self-efficacy can be effective. There is still much to learn about how health care services or pathways should implement support for self-management in a sustainable way and whether this implementation process is different depending on the context or culture of the team or service provided.

Objective: The aim of this study is to tailor and evaluate an intervention (Bridges) to support self-management after stroke in a Swedish context.

Methods: We will use a pretest-posttest design with a case study approach to evaluate the feasibility and implementation of self-management support in two stroke settings. This project includes a complex intervention and depends on the actions of individuals, different contexts, and the adaptation of behavior over time. A mixed methods approach was chosen to understand both outcomes and mechanisms of impact. Data collection will comprise outcome measurements and assessment tools as well as qualitative interviews. Data will be collected concurrently and integrated into a mixed methods design.

Results: Recruitment and data collection for the first site of the project ran from September 1, 2021, to January 17, 2022. The intervention at the first site was conducted from November 1, 2021, to March 5, 2022. The evaluation will start after the implementation phase. The second site has been recruited, and the baseline data collection will start in spring 2022. The intervention will start in early autumn 2022. Data collection will be completed by the end of 2022.

Conclusions: This study represents a unique, highly relevant, and innovative opportunity to maximize knowledge and minimize practice gaps in rehabilitation stroke care. The study will produce robust data on the intervention and in-depth data on the contextual

factors and mechanisms related to the feasibility of the intervention and for whom it is feasible. Bridges has been used in the United Kingdom for more than 10 years, and this study will explore its contextualization and implementation within a Swedish stroke environment. The evaluation will study results at the patient, staff, and organizational levels and provide recommendations for the adoption and refinement of future efforts to support self-management.

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KEYWORDS

self-management; self-management support; self-efficacy; stroke rehabilitation; home rehabilitation; person-centered care

Introduction

Background

Self-management programs are recognized as a valuable approach to supporting people with long-term conditions, such as stroke, to manage their daily lives [1,2]. The essential skills that support successful self-management are also considered critical when navigating the transition from acute illness with structured care in hospital to discharge home [3,4]. However, there is relatively little knowledge and research about how health care services or pathways should implement support for self-management in a sustainable way and whether this implementation process is different depending on the context or culture of the team or service provided [5]. In this study, as part of the SELMA (Self-Management) project, we will tailor and evaluate an intervention developed in the United Kingdom to support self-management after stroke.

Stroke is an acute condition but can have a long-term impact on individuals and families; despite a reduction in the incidence through advances in prevention and emergency care, support for life after stroke and the long-term effects on the individual and families remain inadequate in most health care systems in Europe [6]. Recent health care policy discourses have accelerated efforts to minimize hospital stays and provide more care in the community and the patient's home [7,8], which can be challenging. There are high expectations for individuals and family members to manage their rehabilitation and aftercare, including the coordination of services [9]. In addition, the intensity of services in the community can also be limited [10]. This highlights a real need to initiate high-quality self-management support earlier in the stroke pathway to enable individuals and families to manage the transition from hospital to home and live well after the experience of stroke.

Definitions of what constitutes self-management support vary, but it has been conceptualized as a process in which the person living with a long-term condition, such as stroke, is supported to be an active partner in their recovery process [11]; this definition has been supported by the World Health Organization [12]. Self-management has also been described as a fundamental part of person-centered care [13], which aims to give people opportunities to improve and manage their health according to their beliefs, values, and preferences. Person-centered care also supports the premise that people should be given tools and strategies to recognize and develop their strengths and abilities to live independent and satisfying lives as much as is possible [14-16]. In that sense, the concept of person-centered care is strongly related to person-centered self-management support, which prioritizes and encourages patients to define their health outcomes according to what is most meaningful and important [17]. This is supported by research showing that recovery after a stroke can be enhanced when the person and his or her family or care network work collaboratively with health care professionals and are empowered to define their own goals and activities to support recovery [13].

While there is a move toward more collaborative health care and partnership working models, some critics of self-management programs have highlighted their limitations, particularly when they are professionally led and limited to didactic methods of providing health education to individuals and their families [18,19]. Self-management methods have also been criticized for not reaching groups with low health literacy or cognitive or communication impairments [20-22]. In addition, self-management can be conceptualized as a moral responsibility, contingent on personal agency without considering the person's and family's circumstances, social capital, networks, health literacy, ethnicity, and culture [22].

Given the high numbers of people who experience cognitive or communication problems and mood disorders poststroke [23,24], there is a need to develop self-management programs that are more inclusive and to find creative ways to support individuals' knowledge, skills, and confidence to live well with their condition [25]. According to a Cochrane review in 2016, self-management programs based on the construct of self-efficacy are the most effective in changing people's psychological state and quality of life poststroke [26]. Self-efficacy is a key construct in social cognitive theory [27]. It is defined as people's beliefs about their capabilities to produce designated levels of performance that influence other events that affect their lives [28].

Self-efficacy beliefs can determine how people feel, think, motivate themselves, and behave concerning their health by determining the goals people set, how much effort they invest in achieving those goals, and their resilience when faced with difficulties or failure. Self-efficacy can be considered a mediator and an outcome, and studies have shown a relationship between self-efficacy, activity performance, disability, mood, and quality of life poststroke [29]. Currently, self-management programs that are theoretically informed by behavior change theories, such as social cognitive theory, show a more significant impact [25,26,30].

Self-management support integrated into everyday health care practice could be one way to avoid the constructions and practice

of self-management as an add-on to health care [31-33], but the study of the implementation of programs into service settings, such as a stroke pathway, remains limited. Implementation science is an evolving but established field that provides theories, frameworks, and methodologies for investigating implementation challenges and that contributes to the identification of solutions [34].

The implementation of new ways of working in health care is always context dependent, and careful consideration is required to develop feasible implementation strategies [35]. The intervention in this study is a model of personalized self-management support—Bridges Self-Management (Bridges) [25,31]—and is defined as a complex, as it is characterized by several interacting components that will be implemented in a multidisciplinary team. According to the Medical Research Council (MRC) [35], "An intervention might be considered complex because of properties of the intervention itself, such as the number of components involved; the range of behaviours targeted; expertise and skills required by those delivering and receiving the intervention; the number of groups, settings, or levels targeted; or the permitted level of flexibility of the intervention or its components." The Bridges intervention is a complex intervention because it targets a range of behaviors that include new working methods and may vary greatly across settings in terms of the professional groups involved and patient populations. The SELMA project will explore the process of the implementation of using Bridges. Process evaluation studies can help address how an intervention works and why it does not work in different contexts. Understanding the process and context can help improve fidelity to the core elements that drive an intervention's effectiveness and adaptability to the local context.

As a complex intervention, Bridges [25] focuses on how practitioners interact and support confidence, skills, and knowledge, and it is theoretically informed by principles to support self-efficacy. Health care practitioners support individuals in gaining confidence in self-management using specific strategies and coaching language integrated into everyday practice. First established for stroke, Bridges is feasible in community and acute health care settings. In this study, Bridges will be tailored to the Swedish service setting and evaluated using a mixed methods and process evaluation study design.

Aims and Research Questions

The proposed project aims to evaluate a self-management program intervention and study the implementation process. The specific aims are to explore the following:

1. The feasibility of refining Bridges training for stroke teams and integrating it into Swedish stroke settings.
2. The self-efficacy, health, well-being, self-management, and perceived participation in rehabilitation of patients with stroke pre- and postimplementation.
3. The conceptualization and description of the intervention as a self-management approach by persons with stroke and staff.
4. The ability of the intervention to change the nature of interactions between patients and staff.
5. The critical mechanisms in the implementation process required for integrating self-management support at the individual and ward levels.

Methods

Study Design

We will use a pretest-posttest design with a case study approach to evaluate the feasibility and implementation of self-management support in two stroke care settings. Case studies can provide rich data and are particularly useful when understanding the implementation of a complex intervention in a real-world setting in which the process or context cannot be controlled [36]. As this project includes a complex intervention and depends on the actions of individuals, different contexts, and the adaptation of behavior over time [37], we chose a mixed methods approach to understand both the outcomes and mechanisms of impact. The data collection will comprise outcome measurements by self-assessment questionnaires and qualitative interviews. Thus, quantitative and qualitative data will be collected concurrently and integrated into a convergent mixed methods approach [38].

Normalization process theory (NPT) will guide data collection, analysis, and interpretation [39]. NPT focuses on the work done by staff collectively to understand the processes by which a complex health care intervention is or is not implemented, embedded, and integrated into practice [28]. NPT has been applied in health care settings [40], including stroke care and rehabilitation [40-42], allowing us to compare our findings with previous studies. NPT is a sociologically informed theory of how new interventions in health care and social care are implemented and embedded as normal practice. Its primary focus is on how different groups of participants involved in the process of implementation *work together* to achieve a practice that is being implemented through four fundamental mechanisms that affect whether a new practice or way of working becomes normalized and embedded in everyday practice. These mechanisms relate to activity performed with the following objectives:

1. To make sense of the practice change and gain a shared understanding of the purpose and value of the change and how the new practice differs from previous practice (coherence).
2. To participate and have sustained engagement in the activity (cognitive participation).
3. To successfully work together with the new practice within its setting (collective action).
4. To reflect on and appraise the impacts of the activity in ways that can be used to improve the process for those involved (reflexive monitoring).

In developing the study protocol, we followed the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement [43]. In addition, the description of the intervention follows the Template for Intervention Description and Replication [44]. We also use MRC's guidelines for process evaluation [37], which identify aspects necessary for the sustainability of implementation in various contexts.

Study Phases

The project consists of three phases (Multimedia Appendix 1). The aim of the first phase is to plan the implementation by exploring the usual practice. In this prephase, data about the provision of standard stroke care within the organization in addition to patients' data will be collected to learn about and understand the service within the included organizations; the data will thereby be used to support the implementation of the intervention by the principles of the NPT [39].

To tailor the intervention to the Swedish context, the UK Bridges team will hold additional discovery interviews to explore existing experiences of self-management support, goal setting, and discharge planning methods, as well as any critical issues regarding staff caseloads and organizational challenges. Staff taking part in the training will be asked to provide case studies or personas about patients they are currently working with or have worked with in the past that depict self-management successes and challenges. These case studies will be used to contextualize training in the Swedish setting.

The second phase involves the training of the staff according to the Bridges program, followed by an implementation phase, where the rehabilitation team will implement the intervention (ie, Bridges) in their everyday clinical practice. The implementation phase will last approximately 6 months, which will allow the staff to adopt the intervention and embed it into routine practice. The third phase will involve analysis and reporting on the project's implementation and its outcomes.

Logic Model of the Study

The logic model (Multimedia Appendix 2) that guides the evaluation of the intervention was developed based on the MRC Framework for the Development and Evaluation of RCTs (randomized controlled trials) for Complex Interventions to Improve Health [37] and the NPT [39].

Participating Stroke Units, Staff, and Patients

The study will be conducted at two stroke units in Sweden. We will purposefully recruit stroke units that provide rehabilitation across inpatient and home settings. The 3-year study will be conducted from 2021 to 2023 and will have a mix of multidisciplinary skills.

Participants

The participants in the study will be staff and patients in stroke settings. In regard to the staff, there will be different numbers of staff who carry out the workshop for the intervention depending on the staff size. We expect most people in a staff group to participate. Those who participate are expected to attend all workshops, participate in the discussions, and carry out the intervention tasks. The staff groups will be mixed based on the staff composition of the unit (ie, nurses, physiotherapists, and occupational therapists).

We will also interview approximately 15 staff members in each of the two units to answer questions regarding the organization and integration of self-management in clinical work before and after the implementation of the intervention. The inclusion criterion for the participants in these interviews will be that they should have been working in rehabilitation for at least 6 months.

A total of 40 patients will be recruited prior to the implementation of the intervention in the standard care context (ie, usual rehabilitation), and 40 will be recruited after the intervention has been implemented in the units (20 at each site). As such, the participants in the preintervention patient group will be different from the participants in the patient group after the implementation of the intervention. The inclusion criteria for the persons with stroke will be as follows: aged 18 years of age or older, 3 to 6 months after stroke onset, discharge from rehabilitation at the hospital or day care, fulfillment of the criteria for a clinical diagnosis of stroke, ability to comprehend study goals and procedures, and knowledge of the Swedish language to such a degree that no interpreter will be required. The participants will also identify a family member who will be asked to participate. The time frame of 3 to 6 months after stroke onset was chosen based on the expectation that patients' physical recovery would be stabilized. However, they might still face difficulties in everyday life that have become evident after engaging in daily activities in their environment after discharge.

Recruitment Procedures and Informed Consent

Initially, stroke unit staff from participating stroke units will be asked to identify potential stroke participants based on the inclusion criteria (ie, diagnosis, age, and level of verbal communication). Patients who fulfill the inclusion criteria will receive an information letter; they will be asked if they are interested in participating in the study and if they will allow a person from the research group to contact them. Within 1 to 2 weeks, potential participants will be contacted by telephone, and those who express an interest in participating will be scheduled for an interview. Before the interview, all self-reported instruments will be sent home to the person so they can fill in the questionnaires before the interviews. At the beginning of each interview, the participants will be informed about the study again and will have the opportunity to ask questions. Informed consent will be recorded.

The recruitment of stroke units will be based on suitability (ie, they have home rehabilitation and the teams consists of multidisciplinary professions). The staff at the included sites will receive an information letter about the study, and they will give their written informed consent to participate.

Description of the Intervention

In this project, the intervention is conceptualized as a staged approach to training staff using Bridges and implementing key principles and strategies within everyday practice with stroke patients. The training will be delivered online and weekly using a staged approach across nine sessions, each lasting between 60 and 90 minutes. Every session will cover critical themes, such as emphasizing the importance of the patient's narrative, past life experiences, skills, and assets; enhancing self-efficacy through mastery and vicarious experiences; supporting key self-management skills, such as goal setting and reflection; and exploring hopes and fears as motivators and drivers for action. The staff will have key activities to implement in their work after each session. Individually and collectively, they will agree on strategies for implementation in their everyday work and ways to sustain support for self-management posttraining. The

training will be co-delivered by an experienced health care academic and practitioner and a person with lived experience of an acute and long-term condition. Staff will receive weekly reminders about key aspects of each session and reminders about their targets for putting Bridges into action. They will also receive access to additional resources, such as an interactive handbook, key evidence, posters, and crib sheets. Staff will be provided with support by an internal, educated, self-management facilitator (ie, champion).

Outcomes and Data Collection Methods

Process Evaluation

Data collection to investigate the implementation, feasibility, role of the context, and influencing mechanisms will take place according to the MRC process evaluation [35]. Data will be collected through individual staff interviews, observations, and researcher-reflective field notes to explore factors that might affect the implementation results. The interview guide for the staff interviews was designed to identify factors that may affect the implementation of Bridges. Questions such as "How do you support patients in self-management?" will be asked. Contextual issues, such as leadership, staff ratio, and organization, will be collected by observations, documents, and interviews with staff and managers.

Researchers will take field notes to observe the sessions throughout the intervention process. The notes will contain observations of how the training sessions and communication work. These data will be complemented by interviews with the Bridges team, who will provide the intervention. The interviews will cover experiences of the intervention, such as delivery method, dose, content, and specific components. The interviews will also cover how closely the participants follow the intervention guide.

The experiences of the intervention from the staff's perspective will be collected through interviews after the intervention. The questions will cover experiences of the intervention, such as delivery method, dose, and the content of the sessions. In addition, a sample of interactions between patients and staff will be observed using an observational framework for case studies and implementation studies developed by Morgan et al [45]. For example, the researchers will note where the meeting takes place, who participates, what it is about, and how self-management is addressed. The observations will be complemented with interviews to gather the staff's experiences of their work processes before and after the intervention.

The interviews will be recorded and transcribed verbatim.

Experienced Changes

To explore the staff's experiences of the intervention and any potential changes in working methods after the intervention, interviews will be conducted before and after the intervention. The interviews will be semistructured and will capture the staff's experiences of their work processes and use of self-management strategies in daily work. Questions will cover the work process and how staff support patients' self-management in a person-centered way. In addition, questions about how they support patient participation will also be asked.

We will also strive to capture patients' experiences of how the staff supports self-management and provides opportunities to participate before and after the intervention. Questions will be asked to patients about how they experience the staff supporting them in self-management strategies and the way the staff create opportunities for them to be involved in their care and rehabilitation. The same questions will be asked to each cohort of patients before and after the intervention.

The interviews will be recorded and transcribed verbatim.

Outcomes

We will evaluate outcomes at two time points—pre- and postimplementation of the self-management program—using self-reported measurements and interviews pre- and postimplementation. Data from the staff will be collected before and after the intervention in each setting. Data will be collected from patients and relatives in two cohorts before and after the intervention.

Staff Data

The following demographic data will be collected from the staff: sex, age, professional occupation, number of years in stroke care and rehabilitation, and the participating site.

Qualitative interviews will be completed to explore the staff's knowledge, skills, attitudes, and experiences in performing self-management support. The interviews will be semistructured and conducted before and after the intervention. The questions will capture experiences of self-management and the rehabilitation process as well as how the process affects their work. After the intervention, questions will be added about the experience of the intervention. Issues will specifically focus on how the staff adopt strategies for self-management in their contact with patients. The interviews will also explore the experiences of previous uses and potential news and insights into necessary changes after the intervention. The interviews will be recorded and transcribed verbatim.

Integration of self-management in usual practice will be assessed using the Swedish version of the Normalization Measure Development questionnaire (NoMAD) [46], which measures practitioners' perceptions of the implementation activity level on key NPT-informed domains of work related to the embedding of the intervention: constructs of coherence, cognitive participation, collective action, and reflexive monitoring, as described in the Introduction section. The original version of the NoMAD contains 23 items, and it has been validated across various implementation projects, showing good psychometric properties [46].

Patient Data

We will evaluate outcomes at two time points—pre- and postimplementation of the self-management program—by asking two open-ended questions and using self-reported measurements before and after the implementation. The two questions will be as follows: (1) Can you tell me how the staff supported you in gaining confidence, skills, and knowledge [to self-manage]? and (2) Can you tell me how the staff created opportunities for you to be involved in your care and treatment? In addition, standardized self-reported measures that reflect the mechanism

of impact, such as self-efficacy for self-management measured by the Stroke Self-efficacy Questionnaire (SSEQ) [47], will be used to measure individual confidence in performing activities after stroke. The SSEQ consists of 13 items that measure two separate elements of self-efficacy. Items 1 to 8 reflect self-efficacy in different activities, and items 9 to 13 reflect self-efficacy in self-management. Each item is scored on a 4-point scale, where 0 means "not at all confident" and 3 means "very confident." The answer reflects the stroke patient's confidence in the separate items. The total score ranges from 0 to 39, and this number is then divided by the number of items that have been answered. A higher total score suggests stronger perceived self-efficacy. The scale has been validated and used internationally in self-management studies [31,48].

Perceived health will be measured using a single item from the five-level EQ-5D (EQ-5D-5L) instrument [49], which captures patients' perceived health at the moment. The EQ-5D-5L includes a visual analog scale that records the respondent's self-rated health status on a graduated scale from 0 to 100, with higher scores indicating higher health. In addition, experiences of participation will be evaluated by CollaboRATE [50], a 3-item measure of the shared decision-making process, where items include the following: (1) How much effort was made to help you understand your health situation? (2) How much effort was made to listen to the things that matter most to you regarding your health situation? and (3) When you chose what to do next, how much effort was put into considering what is most important to you? The patients will respond on a scale from 0 ("none") to 9 ("everything").

Additionally, the Stroke Impact Scale-16 (SIS-16) will be employed to assess self-reported physical function [51]. The SIS-16 is a questionnaire focused on quality-of-life levels related to physical function. Thus, persons are asked to rank the difficulty they experienced during the last 2 weeks when performing 16 skills related to four physical domains (ie, strength, hand function, mobility, and activities of daily living); the difficulty is ranked on a 5-point Likert scale, ranging from 1 ("inability to complete the item") to 5 ("not difficult at all"). The scores are transformed on a scale from 0 to 100. A higher score indicates better levels of subjective health-related quality of life. The SIS-16 has shown good psychometric validity in stroke studies [52].

We will also use a specially developed scale for self-management, co-designed with stroke survivors and used across the United Kingdom in stroke improvement work and Bridges [53]. The short questionnaire contains eight questions about how patients experience and understand their situation after stroke and how they can use self-care activities. The patient responds on a scale from 1 ("not at all") to 10 ("entirely"). Example items are as follows: (1) "I understand what caused my stroke," (2) "I understand why my stroke affected me in the way that it has," (3) "Right now, I feel confident that I can cope with the ups and downs that can follow a stroke," (4) "My wishes and priorities were respected when the care staff and I set goals and planned for my care and rehabilitation," and (5) "I feel confident about what I need to do to continue to improve now that I have been discharged from the hospital."

Demographic data such as sex, age, diagnosis, and level of stroke burden will also be collected from participating patients. A detailed data collection plan with all the measures is presented in Table 1 [46-53].

Table 1. Data collection and measurements.

Collected data and methods	Measurements	Sources
Patient characteristics		
Questionnaire	Year of birth, sex, occupation, level of education, living situation, and date of illness	Patient and patient record
Staff characteristics		
Questionnaire	Year of birth, profession, and time employed in the ward unit	Staff
Perceived health		
Questionnaire	EQ-5D-5L[a], 1-100 scale [49]	Patient
Self-efficacy		
Questionnaire	SSEQ[b], 13 items, score 0-3 [47,48]	Patient
Self-management		
Questionnaire	Self-management questionnaire, 8 items, score 1-10 [53]	Patient
Stroke impact on daily life		
Questionnaire	SIS-16[c], version 2.0, 65 items, 5-point Likert scale [51,52]	Patient
Participation and experiences of care		
Questionnaire	CollaboRATE, 3 items, score 0-9 [50]	Patient
Semistructured interview	Interview guide: questions about the staff's daily work in the ward unit, how they are trying to support patients' self-management, and if the way of treating patients has changed postimplementation	Staff
Semistructured interview	Interview guide: focusing on how staff invited patients to be involved in their own treatment and how staff gave support for self-management	Patient
Semistructured interview	Interview guide: questions about how family was involved in the care of the patient and if they saw the staff supporting the patient's self-management	Family
Implementation		
Questionnaire	NoMAD[d]; three sections covering four dimensions of the normalization process theory; rated on Likert scales [46]	Staff
Semistructured interview	Interview guide: investigating barriers and facilitators for introducing the intervention in the ward unit and staffs' views on the implementation process	Staff
Observation	Observation guide: focusing on the activities taking part, who are involved, and in what context	Staff

[a]EQ-5D-5L: five-level EQ-5D.

[b]SSEQ: Stroke Self-efficacy Questionnaire.

[c]SIS-16: Stroke Impact Scale-16.

[d]NoMAD: Normalization Measure Development questionnaire.

Data Management

Anonymized data will be entered into SPSS Statistics for Windows (IBM Corp) [54] and securely stored at Dalarna University, Sweden, according to the rules and guidelines for research at the university and the General Data Protection Regulation. All audio files, including recordings of informed consent, will be stored in a secure file at the university. Names, contact information, and identification numbers will be stored separately from the data.

Analyses

Data will be analyzed between and within the two units, allowing us to understand what factors impact the staff during training and implementation and patients' health and well-being related to the intervention. This will allow us to understand the implementation process of the intervention within a real-world setting and identify the main factors influencing this process.

Data from the questionnaires will be analyzed using descriptive statistics, and the qualitative data from interviews and observations will be analyzed using thematic analysis [55], supported by NVivo software (QSR International) [56]. The acceptability, adherence, and values of the intervention will be described. The intervention logbook, including field notes and transcribed interviews, will be analyzed using qualitative content analysis. In addition, patients' experiences of self-management strategies will be analyzed using qualitative content analysis.

Ethics Approval

Ethical approval was given by the Swedish Ethical Review Authority (2020-02116). Patients and staff have been thoroughly informed of all aspects of the research protocol in which they might be included, and patients have been assigned numbers for anonymization purposes. All data will be collected by phone or using paper questionnaires. Data will be kept in a password-protected database on the research leaders' institutional server, and paper questionnaires will be kept in a locked container at the university.

Results

As of March 2022, the first and second phases were performed at site 1. This means that 20 patients have been enrolled and have completed all baseline measurements. A total of 10 significant others have been interviewed. Observations of the organization and staff interviews have been conducted. The intervention has been performed online by the Bridges team. A total of eight workshops have been conducted online. The researchers have observed workshops, during which they made field notes. Data are being transferred to SPSS and analysis will start when the implementation is completed. However, phase 3 has not started yet, since the implementation had not been completed.

The second site has been recruited, and data collection of baseline data will begin in spring 2022 and will continue for another 6 to 12 months. The intervention is planned to take place in early autumn 2022.

Discussion

Principal Findings

As one of the first studies to examine the feasibility and implementation of a stroke self-management program integrated into a Swedish stroke setting, this study will contribute to (1) a better understanding of the benefits of a self-management approach that specifically targets changing the ways that care providers work with and support patients with stroke and (2) exploring the value of embedding implementation science approaches into the study of complex interventions in stroke, in order to better inform policy makers' decisions about, and implementation of, stroke service delivery.

The qualitative data from the interviews will provide valuable insights as to whether, from a patient perspective, self-management support provided through an adapted Bridges program will reflect greater perceptions of more person-centered care. The study will also provide data to explore whether there have been improvements in perceived health, as well as corresponding improvements according to the underpinning principles and fidelity of Bridges, following a period of staff working in the "Bridges way."

From a clinical perspective, the study will provide new knowledge of whether using a self-management support program based on the concept of self-efficacy and principles to support self-efficacy for self-management will improve rehabilitation through a new integrated way of working into existing health care interactions where people's needs and skills are taken into account during the first interaction. The intervention is integrated into the way of working rather than being perceived as an add-on to care. We hope that the intervention will foster a better anchoring of patients' and families' needs in the rehabilitation process, reducing the risk that the health care professional is the one who defines the problems. In addition, the intervention is intended to favor more active participation by the patient and family and all members of the rehabilitation team; this will be explored through the qualitative and quantitative data from the study.

Having used implementation science approaches throughout the study design, we expect to obtain deep insights into the implementation process from an individual to a macro perspective. Although each of the domains of the NPT may be necessary for ultimate success, health professional associations have a distinct role, from a macro perspective, in both coherence and cognitive participation, essentially in the sensemaking and relational work required to enact change. Considering the NPT at this level may strengthen the theory and suggest unique factors when looking beyond individuals within a team. Findings from this study will inform best practices guidelines by providing empirical data on effective implementation processes of self-management support, both in general and with relevance for scale-up and spread of this approach to other services in the Swedish context.

The dissemination of results will not only take place through academic publications, but will also focus on communicating research results to practitioners and the public in appropriate trade journals, newspapers, and meeting forums, both in face-to-face meetings and online. Dissemination of popular science articles outside the academic world will take place by various members of the research group.

We anticipate that the findings of the study, overall, will address the current call for health care to move toward more self-management and generate new knowledge about what contributes to successful and sustainable self-management support for people with long-term conditions, which is still underresearched in Swedish health care. The project has advantages, as it makes use of existing service time and can be used by all health care professionals in the context of the patient. From a patient perspective, self-management support will mean more person-centered care focused on the patient's ability and opportunity to take an active part in the care of their health in everyday life. The patient will have support beyond that of earlier self-management interventions that relied too heavily on an individualistic approach, and that focused on personal agency without considering personal circumstances, including social capital, networks, health literacy, ethnicity, and cultural aspects [26].

Strengths and Limitations

The proposed study design is a case study design, and the impact on patients' health, well-being, and self-efficacy will need to be tested with a more experimental design. However, our case study research will contribute to a comprehensive and multifaceted exploration of an intervention in a natural uncontrolled setting. We will collect quantitative and qualitative

data to understand the implementation process, context-dependent insights, and the feasibility of the intervention when adapted to the Swedish context.

Conclusions

This study represents a unique, highly relevant, and innovative opportunity to maximize knowledge and minimize practice gaps in rehabilitation stroke care. The study will produce robust data on the effectiveness of the intervention and in-depth data on the contextual factors and mechanisms related to its effectiveness, for whom it is effective, and how it is effective. Participating health care providers will gain the resources to engage patients and families and develop their interprofessional self-management skills, which are crucial to meeting patients' needs and to significantly improving patient self-management support and the rehabilitation process.

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Authors' Contributions

ME, FJ, and TF wrote the first draft of the manuscript. All authors contributed to the proposal and writing of the study protocol. All authors reviewed and revised the final manuscript.

Conflicts of Interest

FJ is the founder and chief executive officer of Bridges Self-Management, a nonprofit organization that is run in partnership with Kingston University and St George's, University of London.

Multimedia Appendix 1
Description of the study phases.
[PNG File , 45 KB - resprot_v11i5e37672_app1.png]

Multimedia Appendix 2
Logic model of the SELMA (Self-Management) project.
[PNG File , 129 KB - resprot_v11i5e37672_app2.png]

Multimedia Appendix 3
Peer Review Report from Forte: Forskningsrådet för hälsa, arbetsliv och välfärd, Sweden (Forte: Swedish Research Council for Health, Working Life and Welfare).
[PDF File (Adobe PDF File), 83 KB - resprot_v11i5e37672_app3.pdf]

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Abbreviations

Bridges: Bridges Self-Management
EQ-5D-5L: five-level EQ-5D
MRC: Medical Research Council
NoMAD: Normalization Measure Development questionnaire
NPT: normalization process theory
RCT: randomized controlled trial
SELMA: Self-Management
SIS-16: Stroke Impact Scale-16
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SSEQ: Stroke Self-efficacy Questionnaire

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Protocol

Physical Activity and Nutrition Intervention for Middle Schoolers (Move More, Get More): Protocol for a Quasi-Experimental Study

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Abstract

Background: Physical activity and nutrition behaviors are important to reducing the prevalence of childhood obesity. Previous research has identified school-based interventions as effective strategies to improve physical activity and nutrition. However, the results are often mixed, and middle schoolers are an under-studied population.

Objective: Our study aims to fill this gap by developing an after-school intervention to increase physical activity and fruit and vegetable consumption that is influenced by national guidelines and formative research.

Methods: This study was an after-school, quasi-experimental study spanning 9 months. Enrollment began in September 2021 and continued on a rolling basis through February 2022. Weekly, middle schoolers were offered 2-3 physical activity sessions and 1 produce kit. Physical activity was measured using accelerometers and questionnaires. Nutrition behaviors were assessed using questionnaires, and physical literacy was assessed using researcher observations. Follow-up data collection occurred in December 2021 and in April 2022. Difference scores will be calculated and analyzed for each outcome variable.

Results: The intervention started in September 2021 and will conclude in May 2022. Published study results are expected in late 2022.

Conclusions: An increase in physical literacy, physical activity, and fruit and vegetable consumption is expected. If successful, future studies will focus on reach and sustainability. Lastly, this study may serve as a model for improving health outcomes in middle schools.

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KEYWORDS

intervention protocol; physical activity; food intake; nutrition; healthy eating; middle schoolers; youth; school; student; fitness; exercise; food consumption; diet; fruit consumption; vegetable consumption

Introduction

Physical inactivity and poor nutrition are strong predictors of negative health status and increase the risk for obesity and other chronic diseases [1]. In the United States, the majority of youth do not meet the national guidelines for physical activity [2] or nutrition [3]. Among middle schoolers—children in 6th to 8th grades—71.3% did not meet the physical activity recommendation of 60 minutes per day of moderate-to-vigorous physical activity [2]. Evidence suggests that the COVID-19 pandemic had additional negative impacts on middle schoolers' physical activity [4]. National guidelines recommend that children and adolescents consume 2.5 cups of vegetables and 2 cups of fruit per day [5]. However, only 7.1% and 2% of

adolescents met the United States Department of Agriculture recommendations for fruit and vegetable consumption, respectively [3]. Consequently, obesity has risen to 21.2% among children and adolescents aged 12-19 years in 2018 compared to 18.4% in 2010 [6].

Schools are an ideal place to promote physical literacy [7] and physical activity to help students achieve physical activity recommendations [8-11], and physical activity in after-school programming is an effective strategy to increase youth physical activity [12-14]. Programming should focus on developing the foundational skills necessary to participate in a variety of activities, as youth who are more physically literate are more likely to be active throughout life [15]. Moreover, evidence suggests that middle schoolers prefer programming that incorporates a variety of sports [16]. Interventions that incorporate sports sampling—the practice of participating in a variety of sports—promote physical activity through adolescence and into adulthood [17,18].

A systematic review by Patrick and Nicklas [19] found that family environment and the availability of fruits and vegetables are strong predictors of fruit and vegetable consumption. However, evidence suggests that school-based nutrition interventions have mixed or limited success in improving fruit and vegetable consumption [20-22] or decreasing BMI [22]. For example, Davis et al [22] found that a gardening, cooking, and nutrition intervention significantly increased vegetable intake, but there was no impact on fruit consumption or BMI. A review conducted by Dabravaolskaj et al [20] found that modifications to school nutrition policies resulted in significant positive consumption for fruit, but not for vegetables. The findings from a systematic review of school-based nutrition interventions suggest that no dominant factor was shared among studies with significant findings [21].

There is convincing evidence that suggests school-based interventions to reduce obesity are effective; however, evaluations of the factors contributing to effectiveness are inconclusive [23,24]. Therefore, the purpose of this study is to describe the study protocol used to evaluate the effectiveness of an after-school intervention on increasing physical activity and fruit and vegetable consumption among middle schoolers in an urban Midwestern US school district.

There are two primary hypotheses for this study. (1) The intervention group will show consecutive increases in physical literacy and physical activity from the baseline in 2 follow-up tests compared to the control group. (2) The intervention group will show consecutive increases in fruit and vegetable consumption from the baseline in 2 follow-up tests compared to the control group. Our secondary hypothesis posits that positive changes in physical literacy and physical activity will be mediated by the intervention dose.

Methods

Study Design

A two-arm, quasi-experimental study was conducted. In an urban Midwestern US public school district, 3 middle schools were identified by the district administration to be included as intervention schools in this study based on need and student population. An additional middle school in the same city with a demographically similar student population was selected to participate as a control. All middle schoolers at the intervention schools were invited to participate in the study. Data were collected during the after-school programming at 3 time points during the academic school year: September 2021, December 2021, and April 2022. All middle schoolers at the control school were invited to participate in a physical activity and nutrition research study. After parental consent and upon enrollment, informed assent was obtained from the middle schooler–participants. The participants then completed a questionnaire assessing demographics, physical activity, and nutrition. Additionally, the participants' weight and height were assessed by research staff to calculate their BMI. Research staff also assessed the participants' physical literacy using the validated PLAYBasic instrument [25,26]. Lastly, all participants were instructed to wear a Garmin Vivofit 4 (Garmin International) accelerometer to track steps and the duration of physical activity for the remainder of the study period. Although moderate- to vigorous-intensity reliability and validity measures were not available for the Garmin Vivofit 4, Garmin wearables are found to be valid and reliable for measuring steps [27]. Coupled with the high acceptability [28] and affordability of the Garmin Vivofit 4, we found it to be a good fit for this study.

Middle schoolers in the intervention group were offered a sport sampling program after school each week throughout the school year. The number of sessions offered was determined by the school's after-school programming schedule. The sport-sampling programming was facilitated by trained coaching staff and rotated sports every 2 weeks. Sport training focused on developing foundational skills and physical literacy and concluded with scrimmaging. Middle schoolers in the intervention group were also offered a weekly distribution of produce. To reduce barriers to participation, the schools offered free transportation home for participants in after-school activities. Middle schoolers in the control group were asked to continue with their regular routines. All participants (intervention and control) were asked to download the Garmin Connect app, given a research team–developed login, and taught how to sync their accelerometer device. Research staff was available to help troubleshoot syncing issues and sync the participants' accelerometers during school visits if they were unable to sync their accelerometer using a personal smartphone or tablet. All participants repeated the baseline testing after approximately 3, 6, and 9 months.

Ethics Approval

All study procedures were approved by the University of Missouri-Kansas City Institutional Review Board (#2017528).

Participant Recruitment

All middle schoolers at the participating schools were eligible to participate in the study. Recruitment began in September 2021 and continued on a rolling basis through February 2022. Recruitment efforts required a multimodal strategy: direct recruitment, snowball sampling, and referral recruitment. Research staff attended school lunches and district enrollment events to directly enroll students. Financial giveaways aided

enrollment interest during in-person recruitment. Students had the opportunity to aid researchers by recommending peer groups for recruitment or referring friends directly to the program.

Power Analysis

The sample size needed to understand if the intervention will have an effect was calculated using G*Power (version 3.1.9.4; Heinrich-Heine-Universität Düsseldorf) [29]. A systematic review of physical activity interventions suggested that similar interventions have significant but small effect sizes (0.44, 95% CI 0.19-0.70) [30]. A review of school-based nutrition interventions on behavior suggested that the average intervention has a small effect (0.33, 95% CI 0.55-1.10) on adolescent BMI [31].

Based on a *P* value of <.05 and physical activity interventions having a small effect size of 0.44 on outcome measures, this study requires a minimum of 47 participants to understand the differences between matched pairs for physical activity behavior. Based on a *P* value of <.05 and nutrition interventions having a small effect size of 0.33 on the consumption of fruits and vegetables, this study requires a minimum of 90 participants to understand the differences between matched pairs for fruit and vegetable consumption. We expected a 20% attrition that is similar to other school-based health behavior interventions [32]. Therefore, a minimum of 108 middle schoolers would need to be recruited through the participating schools (control and intervention).

Description of the Intervention

Overview of the Program

"Move More, Get More" was an after-school intervention targeting physical activity and nutrition for urban middle schoolers at select middle schools in the Kansas City Public School District. The program was designed following national physical activity and nutritional guidelines and evidence from previous research. The programming was further influenced by the formative research conducted by the research team [16]. Key research findings centered on the promoters and barriers to physical activity and fruit and vegetable consumption, both before and during the COVID-19 pandemic. Parents and students from these focus groups made recommendations that guided program development. To increase physical activity, parents and students recommended opportunities for competition, goal setting, and financial incentives [16].

The program duration was set for 9 months, from September 2021 through May 2022, following Kansas City Public School District's academic calendar. Baseline data were collected at the time of enrollment (from September 2021 to February 2022) and follow-up data collection occurred in December 2021 and April 2022. Session frequency and duration were dependent on each site's after-school transportation availability and dismissal schedule. The session frequency and duration at the 3 sites were as follows: 3 sessions/week for 1-hour sessions, 3 sessions/week for 2-hour sessions, and 2 sessions/week for 1-hour sessions.

Physical Activity Programming

Sessions were designed to achieve 1 hour of moderate-to-vigorous physical activity daily, per the Centers for Disease Control and Prevention's physical activity guidelines for youth [8] and were held at the students' school. Sessions were hosted immediately after school in accordance with the school's other after-school programs. Evidence from our formative research suggested that physical activity sessions would be more successful if they included opportunities for fun, peer influence, competition, goal setting, and incentives [16]. Additional findings suggested that time constraints, the overcompetitive nature of sports programs, and decreased motivation and access to physical activity were barriers to physical activity [16]. As a result, we designed the programming with the following aims: introduce a variety of sports and the skills necessary to participate in a variety of sports; encourage peer interaction by implementing snowball recruitment and focusing on team-oriented sports; provide opportunity for team competition through scrimmages and for goal setting and individual competition through step challenges using accelerometers. Incentives were used to increase motivation, encourage consistent participation, and facilitate thorough data collection. Furthermore, programming focused on skill development and inclusiveness and limited overcompetitiveness by implementing no-cut policies.

At the beginning of each semester, the program manager created a template schedule of sport and team activities, with activities rotating every 2 weeks. Activity types included traditional sports (basketball, soccer, football, etc), team-based activities (capture the flag, dodgeball, etc), dance, yoga, and others. This schedule was adapted by each intervention site's coach based on their expertise, space, equipment availability, and student interest. For sport-based activities, fundamental and basic skills were taught during the sessions. During the last day of each unit, the participants would engage in scrimmage play. Each session included a 10-minute warm-up, an activity spanning 40-100 minutes, and a 10-minute cooldown.

Physical-activity coaches were primarily contracted through partnering organizations that are trusted and established within the school's surrounding community (ie, community services center, parks and recreation department, and sport performance training center). Coaches were required to have previous experience leading youth physical activities. All staff completed mandated reporter training and a background check through the school district. Intervention sites were assigned 2 coaches and 2 or 3 researchers during each session. A staff-to–middle schooler ratio of 2 to 30 was required for all sessions.

Nutrition Programming

Nutrition programming aimed to increase fruit and vegetable consumption toward meeting national guidelines. Furthermore, evidence from a systematic review suggested that family environment and availability are strong predictors of fruit and vegetable consumption [19] and cooking from home is associated with several nutritional benefits for youth [33]. Moreover, our previous findings suggested that parental control of nutrition behaviors and presentation, preparation technique, and convenience are all important factors to increasing fruit and vegetable consumption [16]. As a result, produce kits were distributed weekly to all middle schoolers.

Produce distributions were provided by University Health's Healthy Harvest Mobile Market, a converted city bus designed to deliver fresh, healthy foods throughout Kansas City, Missouri. Each weekly distribution was procured to create at least one meal for a family of 5. Each bag included recipe staples (ie, onions, potatoes), recipe-specific produce, popular fruits, and occasionally unique fruits or vegetables middle schoolers may not ordinarily be exposed to. In addition to produce, University Health provided recipe cards, nutrition information, and food preparation techniques for at-home cooking. The produce bags were valued at approximately US $20.

Control Group

Middle schoolers were invited to participate in the research study during physical education classes over a period of 2 weeks. Enrollment was conducted during each grade level's physical education period over the span of 3 weeks. Control enrollment was identical to intervention data collection practices. All participants were asked to wear the accelerometer devices continuously throughout the study period. Participants in the control group were asked to continue their normal, routine activities. Control data collection took place during scheduled youth physical education classes.

Incentives

Intervention participants received a US $25 gift card after completing baseline testing (questionnaire and objective measurements) and an additional US $25 gift card for each additional completed assessment at the 3- and 6-month time points. Participants in the control group received a US $10 gift card after completing baseline testing (questionnaire and objective measurements) and an additional US $10 gift card for each additional completed assessment at the 3- and 6-month time points. Since a participation component and larger time commitment was expected among the intervention group, we provided larger monetary incentives for the intervention group.

Measures

Demographic Variables

Middle schoolers' demographic variables were assessed using a self-report questionnaire in the baseline test. Middle schoolers were asked their sex assigned at birth, birth date, race by selecting all that apply (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White), and ethnicity (Hispanic or Latino) by indicating yes or no.

Physical Activity

Self-reported physical activity was assessed using the International Physical Activity Questionnaire Short Form, which assesses physical activity using a 7-day recall to estimate moderate- and vigorous-intensity physical activity, walking, and sedentary behavior [34]. All values were reported in minutes per week.

All middle schoolers were given a Garmin Vivofit 4 accelerometer to objectively measure physical activity throughout the study period. A valid day is defined as a middle schooler having ≥8 hours of wear time between 9 AM and 9 PM and ≥500 steps. To account for nonwear time, we considered 3 consecutive epochs of ≥15 minutes with a maximum motion intensity value of 0 as nonwear time. Daily data were aggregated at the weekly level for each participant; ≥1 valid day is required for the week to be included in the analyses. Garmin accelerometers automatically record moderate-to-vigorous physical activity; the feature is activated when the user walks for ≥10 minutes or runs for ≥1 minute.

Dietary Behaviors and Fruit and Vegetable Intake

The selected questions were adapted from the 2019 National Youth Risk Behavior Survey for high schools that asked about fruit, vegetable, soda, and sport drink consumption in the past 7 days [35]. The original response options ranged on a 7-point scale from no consumption to >4 times a day; our survey collapsed the response options into a dichotomous yes-or-no format, as directed by the funding agency.

Height, Weight, and BMI

Height and weight were assessed objectively by trained research assistants using a validated scale [36] and stadiometer [37]. BMI was calculated with the following formula: $BMI = weight\ (kg)/\ (height\ [m])^2$.

Physical Literacy

Trained research staff assessed physical literacy using the PLAYbasic instrument [26], which assesses the physical abilities of participants in 4 domains: balance, throwing, kicking, and locomotor. Staff asked the participants to perform 5 tasks: (1) run to a cone approximately 5 meters away, turn around, and run back to the starting point; (2) hop to the same cone on one leg, turn around, and hop back on the other leg to the starting point; (3) throw a tennis ball overhand to a wall 1.5 meters away and have it bounce back over their head; (4) kick a ball to a wall 4 meters away over a 1-meter line from the ground; and (5) walk backward toe to heel in a straight line for 2 meters. Each task was scored on a 0-100 scale with 0 being no proficiency and 100 being completely proficient. The scores were also categorized into the 4 rankings: initial (score of 0-25), emerging (score of 26-50), competent (score of 51-75), and proficient (score of 76-100); scores of 0-50 represent the developing rating, and scores of 51-100 represent the acquired rating. A final score was calculated by adding the section scores and then dividing by 5 according to the scale's instructions [26].

Statistical Analysis

SPSS Statistics for Windows (version 26; IBM Corp) will be used for data analysis. Univariate statistical analyses will be conducted for all study variables. Difference scores will be calculated for each outcome variable. Subsequently, a series of repeated measures analysis of covariance will be conducted to assess within-group differences, while controlling for school and other factors. To assess the dose response relationship between intervention attendance and the outcome variables, linear and logistic regression models will be conducted. An alpha level of 95% will be used for all analyses.

Results

This study started in September 2021. Formative research to inform the intervention was conducted in December 2019 and from June to August 2020. The in-person intervention implementation was delayed until September 2021. As the study had a rolling enrollment period, we completed all baseline testing by November 2021. The results of the study will be communicated to the research and professional community via publications. We will communicate the results with other stakeholders (eg, community partners, parents, school staff, etc) via newsletters, social media posts, website, and local media.

Discussion

Expected Findings

As childhood obesity rates increase [5], it is important to expand access to noncompetitive, school-based physical activity programming and promote fruit and vegetable consumption. School-based interventions that reduce common barriers (eg, fees, transportation, competitiveness) are ideal to improving youth population–level health. Fostering foundational physical literacy skills [15] and increasing access to physical activity programming are necessary for youth to be and remain physically active through life [38] to prevent obesity and related chronic diseases [1]. In response, this study tested the effectiveness of the "Move More Get More" program for middle schoolers using a quasi-experimental study. More specifically, this study investigated whether the program could increase the middle schoolers' physical literacy, physical activity, and fruit and vegetable consumption. Furthermore, we investigated the dose-response effects of the intervention.

Similar to other after-school physical activity interventions [12-14], we expect participants would have significantly increased their physical literacy and moderate- to vigorous-intensity physical activity. Few school-based interventions have resulted in increases of fruit and vegetable consumption [20-22]; therefore, this study will add to the literature by evaluating a novel nutrition intervention. Since the access and availability of fruits and vegetables is a predictor of consumption [19], we expect that youth would have significantly increased their consumption of fruits and vegetables at the first and second follow-ups compared to the baseline testing. We also expect greater increases in physical literacy and physical activity with greater attendance at the physical activity programming. In recent years, physical literacy has emerged as a core construct within public health [15]. Therefore, our findings will contribute significantly to the scholarship regarding interventions to increase physical literacy and the association between physical literacy and increased physical activity.

Adopting healthy behaviors in adolescents is important for maintaining healthy behaviors as an adult. However, adolescents in the United States are increasingly inactive and do not meet fruit and vegetable consumption recommendations. The "Move More, Get More" program has the potential to reach large proportions of a student body, unlike competitive sports, which is often the norm. Interventions accessible to all students at a school may be one strategy to increase physical activity and nutrition behaviors for middle schoolers.

Limitations and Strengths

This study design has several limitations. First, schools were selected based on student need and demographics and were unable to be randomized into the intervention or control group. Consequently, the findings may be due to differences among school or student characteristics rather than the intervention. This limitation highlights the importance of documenting issues related to these characteristics and the need for a process evaluation plan. This study is also limited by relying on several self-report measures and by the measures' ability to detect variability. For example, nutrition measures asked participants if they consumed the target variable yesterday and provided the following response options: yes, no, and not sure. These questions were required by the grantor, and, to limit the questionnaire size, we did not add additional measures that could potentially detect more variability and changes in participant behavior.

A major strength of this study is that the intervention was developed based on the results of our formative research via focus groups with both middle schoolers and parents, which included the middle schoolers and parents that attend the targeted middle schools [16]. Other strengths of this study include the potential to recruit a large, diverse sample. Further, this study sample is specific to middle schoolers, a population that is under-studied but represents a pivotal time in an adolescent's development of health behaviors. Lastly, this study used accelerometers to objectively measure physical activity as opposed to relying on student self-report data, which may be biased.

Future Directions

If the intervention is proven to be effective to increasing physical literacy, physical activity, and fruit and vegetable consumption, our future research will focus on the reach and sustainability of the intervention. Further research is needed on how physical activity interventions are implemented and scaled [39-42]. This study can serve as a model for local and national programming to tackle childhood obesity.

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Authors' Contributions

AG and JSL conceptualized the study and contributed to manuscript writing. KE, BDW, MB, and EV contributed to writing the manuscript.

Conflicts of Interest

None declared.

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Protocol

Implementation of a Brief Dialectical Behavioral Therapy Skills Group in High Schools for At-Risk Youth: Protocol for a Mixed Methods Study

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Abstract

Background: Adolescence is a developmental period marked by engagement in risk-taking behaviors, especially among impulsive or emotionally dysregulated youth. Thus, interventions that teach skills to reduce the risk of negative outcomes associated with emotional dysregulation are required. Social and emotional learning (SEL) programs have been developed to address both adolescent emotional dysregulation and risk-taking behaviors; however, current programs have mostly been implemented among younger youth and are used as a tier 1 universal intervention rather than a targeted tier 2 intervention for youth identified with emotional regulation difficulties.

Objective: This study aimed to address the need for SEL programming that can be delivered in schools, particularly for older youth who have difficulties with emotional or behavioral dysregulation, to reduce the risk of health-risk behaviors among this population.

Methods: Here, we outline the implementation of an SEL intervention titled *Going 4 Goals*, a 9-session adaptation of the Dialectical Behavioral Therapy for Adolescents (DBT-A) program delivered to at-risk high school students in a school setting. The primary objectives of the study are to test whether participating in the skills group intervention produces significant increases in the core DBT-A skills of mindfulness, emotional regulation, distress tolerance, and interpersonal effectiveness, while also producing significant decreases in substance use and risky behaviors. These primary outcomes are based on changes in participant scores between baseline and after the intervention and follow-ups at 1, 3, and 6 months compared with a control group of youth participating in the school's health curriculum at the same time points. Qualitative interviews will also be conducted with intervention participants and school staff to examine acceptability and facilitators of and barriers to the intervention.

Results: A total of 171 participants across 13 groups had been enrolled in the intervention, with data collection ending December 2021. Data analysis will begin in the spring of 2022, with expected results to be published in the spring of 2023.

Conclusions: This paper describes the protocol of the 9-session school-based adaptation of the DBT-A intervention and discusses the strengths and limitations of the study and future directions.

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KEYWORDS

dialectical behavioral therapy; adolescents; high school; intervention; high school; teenagers; risk-taking behavior; impulsivity; emotion dysregulation; social and emotional learning; youth

Introduction

Background

Adolescence is a developmental period characterized by an increase in risk-taking behavior [1-3] manifested in several areas, including reckless driving, unprotected sexual behavior, and substance use [4]. Although an increase in some risk-taking behaviors is common among adolescents, addressing engagement in such behaviors is warranted because they are associated with the leading causes of death among adolescents (eg, injury deaths from motor vehicle crashes, firearms, and suffocation) [5]. In addition, adolescents who experience higher emotional dysregulation and impulsivity are especially vulnerable to the negative health outcomes of risky behaviors [6,7].

Social and emotional learning (SEL) programs have been developed to primarily address adolescent emotional dysregulation and risk-taking behaviors within school settings [8,9]. The term SEL was first coined in 1994 when the Collaborative for Academic, Social, and Emotional Learning (CASEL) was founded [10]. Through SEL programming, youth can acquire and effectively apply the knowledge, attitudes, and skills necessary to understand and manage their emotions, establish and achieve positive goals, develop and maintain positive relationships, and make healthy and responsible decisions [10]. In turn, this knowledge and skill development aids in youth's ability to attain and maintain personal well-being across their life span [10]. Thus, the core components of SEL programs that align with the five competencies identified by the CASEL focus on improving (1) self-awareness of one's emotions, thoughts, and behaviors; (2) self-management to regulate one's emotions, thoughts, and behaviors effectively; (3) social awareness and skills; (4) relationship skills to form and maintain healthy relationships; and (5) responsible decision-making to make constructive and respectful choices [11-13].

SEL programs have been associated with multiple positive outcomes, including increases in social skills and prosocial behaviors and decreases in antisocial and externalizing behaviors among youth [14-17]. For example, a meta-analysis of postintervention and long-term outcomes of school-based SEL programs among youth in elementary, middle, and high schools found that participants who received the intervention had better outcomes than those in the control group at postintervention on social-emotional skills, social-emotional attitudes toward self, others, and school, emotional distress, academic performance, and drug use (effect size=0.12-0.22). These improvements were also found in follow-up assessments occurring between 6 months and 18 years after the intervention for all outcomes as well as prosocial behaviors and conduct disorder (effect size=0.13-0.33) [17].

Despite the clear benefits of SEL programs on health outcomes for youth, there are gaps in the generalizability of the findings. First, research on the implementation of SEL programs has been primarily conducted among younger youth (eg, in elementary or middle school) [16], with limited research testing the efficacy of SEL programs among older youth in high school settings [18]. For example, of the 213 studies included in a meta-analysis conducted by Durlak et al [16], only 13% were from high school settings, with a similar percentage of studies found in the meta-analysis conducted by Taylor et al [17]. Second, there is limited empirical evidence on the efficacy of SEL programs as targeted interventions (also referred to as *tier 2* interventions) for youth experiencing social, emotional, or behavioral problems and at increased risk of negative health outcomes [19]. For example, Blewitt et al conducted a systematic review of targeted tier 2 SEL interventions and found that only 19 studies met the inclusion criteria. However, the findings indicated positive outcomes, with the tier 2 SEL programs strengthening participants' social and behavioral functioning [19]. Yet, the findings are limited in generalizability in that the review focused only on tier 2 SEL programs delivered in early childhood education and care settings, with much of the evidence directed primarily toward preschoolers with externalizing problems. Thus, there is a gap in the literature regarding the efficacy of tier 2 SEL interventions for older at-risk adolescents.

Dialectical behavioral therapy (DBT) is an effective tier 2 SEL intervention for social, emotional, and behavioral problems among youth in high schools. DBT was originally developed by Linehan et al [20] to treat chronically suicidal adults, many of whom were diagnosed with borderline personality disorder [20]. DBT uses cognitive behavioral and mindfulness techniques to address difficulties in four specific areas—distress tolerance, mindfulness, emotional regulation, and interpersonal effectiveness—and has been proven to be effective in treating many mental disorders [20-22]. Owing to the success of the intervention among adults, adaptations of DBT have been created for adolescents, particularly those with similar clinical symptoms or difficulties with emotional dysregulation [23,24]. The format of both DBT and Dialectical Behavioral Therapy for Adolescents (DBT-A) consists of individual therapy and a skills group component; however, DBT-A differs from DBT in that some content is adapted to be developmentally appropriate for youth, and the length of treatment is reduced from 1 year to 24 weeks [23,24]. Outcome data for DBT-A have demonstrated the effectiveness of the intervention in treating various mental and behavioral health conditions in adolescents, including suicidality, emotional dysregulation, depression, and anger across multiple clinical settings, including correctional facilities, residential in-patient programs, and day treatment programs [23,25,26].

DBT-A has also been adapted for implementation in nonclinical settings, such as schools, with the publication of the DBT Skills

in Schools: Skills Training for Emotional Problem Solving for Adolescents (DBT STEPS-A) manual [27,28]. In the DBT STEPS-A manual, the authors positioned DBT as an SEL curriculum given its focus on understanding and managing emotions, developing and maintaining relationships, and responsible decision-making, which align with the CASEL principles [27,28]. A critical limitation, as also noted by other scholars, is that of the many existing SEL interventions, there is a lack of explicit attention to emotional processing, such as learning how to cope, regulate emotions, or modify factors causing emotional distress [29], which is a key component of DBT interventions. In addition, the authors of the DBT STEPS-A manual discuss the use of the program as both a universal tier 1intervention—for all students, delivered within a classroom curriculum—and a targeted tier 2 intervention for students who need additional support for their social and emotional needs delivered in small groups [27,28].

However, few studies have examined the efficacy of DBT-A or DBT STEPS-A in school settings or as targeted tier 2 interventions. To our knowledge, only 6 studies have been published, 5 of which were conducted among high school youth. It is also important to note that 3 of the studies were conducted before the publication of the DBT STEPS-A and were therefore conducted using an adaptation of the DBT or DBT-A protocol. The remaining 4 studies used the DBT STEPS-A manual. Notably, all studies included only the group skills component and modified the length of treatment to 6 to 22 sessions across 4 to 22 weeks.

The first study was conducted by Richard et al [30], who adapted the original DBT skills group protocol created by Linehan et al [20] to address the behavioral distress needs of youth in a disciplinary alternative education program. The protocol included 8 to 10 group sessions lasting 40 to 45 minutes, which occurred twice a week for 4 weeks. Their study included 125 students aged 6 to 18 years who primarily identified as Hispanic. The findings indicated that participation in the group was associated with reductions in behavioral distress compared with youth who did not receive the intervention [30]. A second study by Zapolski and Smith [31] also found promising results for at-risk middle school youth. Similar to the Ricard et al study [30], Zapolski and Smith adapted the original DBT skills group for adults by Linehan et al [20] to a 9-session skills group protocol for middle school youth. Among the 53 students (most in seventh grade, mean age 12.7 years who participated in the group, the findings indicated that the intervention effectively decreased self-reported engagement in risky health behaviors and intentions to engage in risky behaviors. Moreover, these findings were more pronounced among youth who reported higher impulsivity scores [31].

A third study published by Flynn et al [32] differs from the first two in that it was conducted outside the United States, in Ireland, and used the DBT STEPS-A manual [27]. Moreover, the researchers adapted the DBT-A program to be delivered across 22 weeks rather than 30 weeks, as originally proposed by Mazza et al [27] Positive outcomes were found, such that among their sample of 72 girls aged 15 to 16 years, participation in the group intervention was associated with significant improvements in emotional distress symptoms and internalizing problems compared with a control group of youth who did not receive the intervention [32]. The fourth study, by Martinez et al [33], also implemented the DBT STEPS-A manual [27] and was conducted with 42 ninth grade students enrolled in a rural southeastern high school in the United States. The program consisted of 20 sessions delivered across 12 weeks, and the findings indicated a treatment effect. Participants in the intervention reported significant improvements in social resiliency and difficulties with emotional regulation compared with youth in the control group (ie, required health or physical education course). The fifth study, which was also conducted in the United States but within low-income schools, was published by Chugani et al [29]. The program was adapted to 19 sessions delivered primarily once a week in high schools within a large northeastern school district. Although the study did not focus on student outcomes, the findings indicated high acceptability and feasibility among teachers conducting the intervention in schools within the health curriculum.

Although promising data exist based on the studies cited, there have also been mixed findings. Burckhardt et al [34] adapted the original DBT protocol for adults [20] to a 6-session skills group, with each session lasting 50 minutes. The results indicated, among their sample of 50 youth aged 14 to 16 years, that participation in the intervention was associated with small *increases* in anger, symptoms of anxiety, and depression based on both the postintervention and 6-month follow-up assessments. The researchers hypothesized that this finding could be related to the focus on mindfulness in DBT and the ability to *open up*, which may result in greater awareness, and thus the reporting of symptoms of anxiety and depression. This study also indicated that the control group, which consisted of youth who attended usual classes that involved learning material regarding future careers, had better emotional regulation scores than the intervention group [34]. However, some positive findings were observed for the intervention group based on qualitative interviews conducted among participants—74% of them reported positive benefits of the intervention, including being able to better regulate their emotions.

In conclusion, despite the benefits of SEL programs for adolescents in reducing the risk of engagement in risk-taking health behaviors, much of the existing empirical support for SEL programs is based on evidence from younger youth and has rarely been tested as a tier 2 intervention targeting youth at greater risk of experiencing adverse health outcomes. Using DBT-A can address these gaps by providing an evidence-based intervention that shows promise in addressing risk-taking behavior among older at-risk youth in school settings. However, research implementing DBT-A in schools for older youth, particularly as a tier 2 intervention, is limited, and more empirical support on its efficacy is needed.

Objectives

In this study, we aim to fill this critically important research and clinical gap by implementing a 9-session adaptation of the DBT-A [24] and DBT STEPS-A [27] manual, titled *Going 4 Goals*, in 2 public high schools for at-risk youth identified by school staff. The primary objectives of the study are to test whether participating in the skills group intervention produces

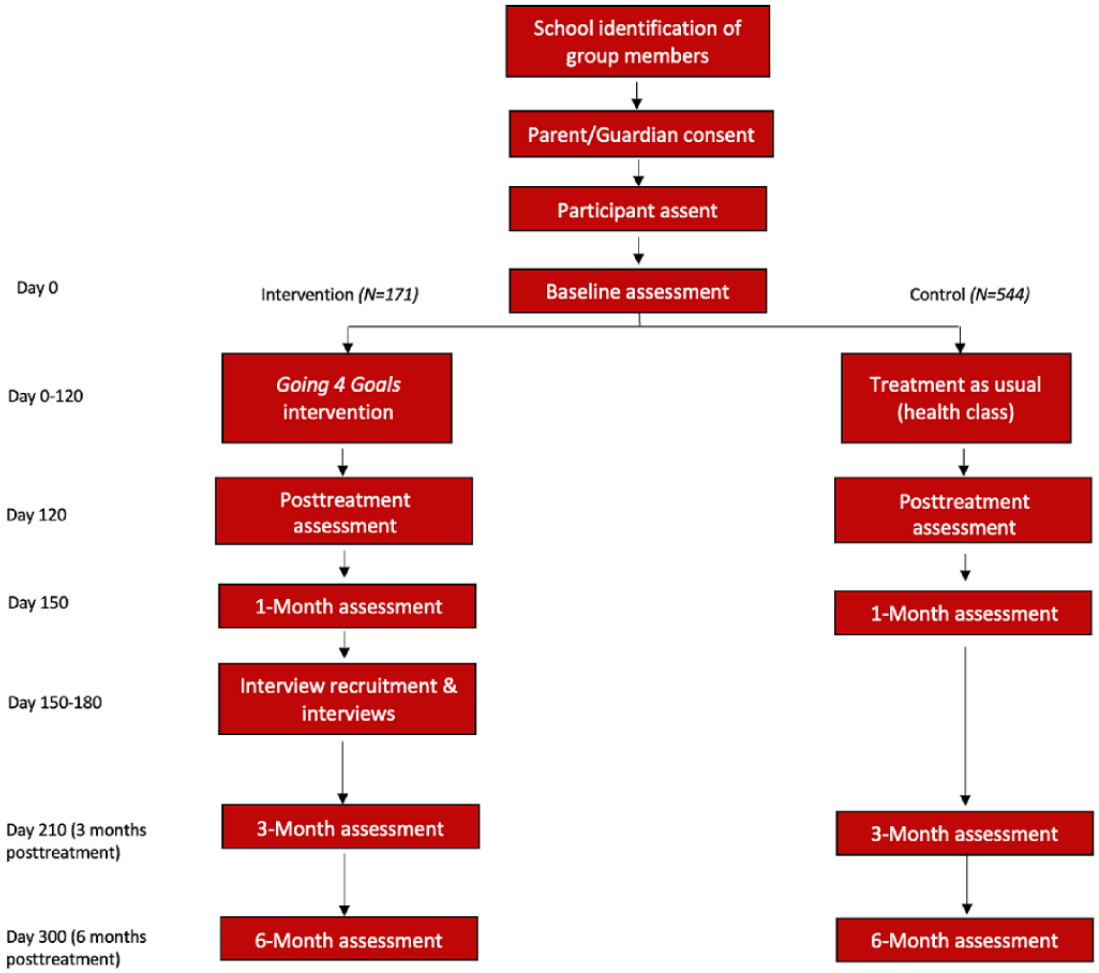
significant increases in core DBT-A skills (ie, mindfulness, emotional regulation, distress tolerance, and interpersonal effectiveness) and significant decreases in substance use and risky behaviors. These outcomes are based on changes in participant scores between baseline and postintervention assessments and 1-, 3-, and 6-month follow-ups compared with a control group of youth participating in the school's health curriculum at the same time points. A secondary objective is to examine the acceptability, facilitators, and barriers of the intervention through qualitative interviews with intervention participants and school staff. This paper describes the protocol of the 9-session school-based adaptation of the DBT-A intervention.

Methods

Study Design Overview

A mixed methods design was adopted to explore the implementation and efficacy of the school-based DBT-A skills group, titled *Going 4 Goals*, for at-risk high school youth. Youth are identified by school staff to participate in the skills group, which is being held during school hours at local high schools and occurs during noncore instructional class periods. An opt-out consent process for guardians and an active assent procedure for youth is being used, with all eligible participants included in the intervention groups. Control participants are also being enrolled to compare outcomes. Control group students are from health classes at the school where the intervention is taking place. All participants (intervention and control) will take a quantitative survey at 5 time points (baseline; after the intervention, ie, approximately 9 weeks after baseline; and 1, 3, and 6 months after the intervention) on paper or electronically through Qualtrics, a secure research survey software provided through the university. The survey includes measures to evaluate the core skills of the DBT-A program: emotional dysregulation, distress tolerance, mindfulness, and interpersonal effectiveness and other key study variables, including impulsivity, substance use, and risk-taking behaviors. At the completion of each 9-session intervention program, participants and school staff will be asked to participate in a qualitative interview approximately 1 month postintervention to understand the facilitators and barriers to the program. The study was approved by the Indiana University–Purdue University Indianapolis institutional review board (#1610685795) on July 25, 2018. Data collection began in July 2018 and ended December in 2021. Figure 1 illustrates the implementation timeline. Details regarding the methodology of the study protocol are provided in the subsequent sections.

Figure 1. Study flow.



Study Recruitment

The principal investigator and project manager reached out to several schools in the Indianapolis area to inquire about their interest in partnering to implement the *Going 4 Goals* program with their students. Two schools agreed to implement the intervention during school days. Both schools are diverse, with high rates of free or discounted lunch recipients (76% and 50.1%, respectively) and median household incomes of US $49,175 and US $62,829, respectively. Both schools are also diverse in relation to race and ethnicity, with approximately 70% of the students at both schools identifying as non-White. Intervention participants are identified by the school staff based on who they deem as either *at risk* (eg, prior school-related drug offense, conduct problems, engagement in risky health behaviors or school fights, or had in-school or out-of-school suspension) or believe could benefit from learning the core DBT-A skills (ie, mindfulness, emotional regulation, distress tolerance, and interpersonal effectiveness). The most common identification measures used by schools are (1) teacher recommendation based on class attendance and student behavior in class and (2) guidance counselor recommendation based on student behavior referral records (ie, number of detentions, suspensions, or expulsions on students' records), attendance records, or known substance use.

Consent and Assent

Parent or guardian approval is being used based on an opt-out parent or guardian consent process. A letter is sent to the identified youth's legal guardian on behalf of the school and the research team, indicating that their child has the option to participate in a group that aims to reduce the risk of substance use and other risky health behaviors by teaching skills to help manage emotions, stress, and interpersonal conflicts. The letter describing the study's purpose, risks, benefits, and inclusion and exclusion criteria (ie, students are enrolled in the school; are able to adequately speak, understand, and read English; and are not concurrently receiving mental health services for the duration of the intervention program) is sent to the guardian through the US mail or sent home by the school administration with each student. The legal guardian is asked to sign and return to the bottom of the letter if they do not want their child to participate in the intervention. Guardians are given 2 weeks to return the opt-out consent form. After the 2-week period for guardians to return consent forms has passed, all youth who are still eligible are asked to attend an information session regarding the intervention group during school hours. A brief overview of the intervention is provided, and the youth who wish to participate sign assent forms and complete a survey assessing baseline measurements of the study variables. Participants are also informed about the opportunity to complete a qualitative interview after completing the skills group to understand the facilitators and barriers of implementation. For participants who wish to participate in the interviews, a new assent form is provided and signed by them at the end of the intervention to record and transcribe the interviews.

Control participants complete a similar consent and assent process. A consent form is sent home to their parent or guardian with a 2-week window to return it to the school before the youth can assent to participate in the study. Those youth who consent are then asked to complete the survey at school during their health class.

Ethical Approval and Consent to Participate

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was approved by the Indiana University–Purdue University Indianapolis institutional review board (#1610685795). Opt-out consent for participation will be obtained from the youth's legal guardian. Written voluntary informed consent will be obtained from all youth participants. Confidentiality will be maintained, except if participants are at risk of significant harm or request assistance.

Intervention Procedures

Going 4 Goals

Youth who participate in the *Going 4 Goals* group intervention will attend 9 sessions conducted once a week during school hours, lasting approximately 40 minutes (ie, 1 class period). The intervention sessions were first taken from the DBT-A manual [24], which provided 2 sessions for the mindfulness and 4 sessions for the emotional regulation, distress tolerance, and interpersonal effectiveness modules. To reduce the material to fit within a 9-session intervention, the principal investigator of the study consulted with other clinical psychologists trained in DBT to identify the primary skills related to the 4 DBT components that could be delivered within nine 40-minute sessions. The selected skills and text discussing them were then taken directly from the DBT STEPS-A manual [27] to align with how the skills would be presented to students within a nonclinical school setting. To this end, of the 9 sessions, the first was devoted to orientating the students to the intervention, goal setting, and introduction to mindfulness, the second session was devoted to mindfulness skills, the third through fifth sessions were devoted to emotional regulation skills, the sixth and seventh sessions were devoted to distress tolerance skills, and the eighth session was devoted to interpersonal effectiveness skills. The ninth session reviewed all skills learned in previous sessions and included the postintervention assessment. Each session begins with a mindfulness exercise and a didactic period in which skills related to emotional regulation, distress tolerance, interpersonal effectiveness, and mindfulness taken directly from the DBT STEPS-A manual are taught. There is also time incorporated within each session for active youth participation, with at-home practice assigned at the end of each session. See Textbox 1 for a complete overview of the sessions and objectives.

Textbox 1. Going 4 Goals session overview.

Sessions and their objectives

- Session 1: Introduction
  - Give students an overview of the program and its purpose.
  - Present the rewards system to the students for attainment of each goal.
  - Complete pretreatment survey.
  - Mindfulness introduction.
- Session 2: Mindfulness skills
  - Teach students how to be aware of their emotions without necessarily changing them.
- Session 3: Understanding emotions
  - Teach students how to observe and describe emotions.
  - Help students understand the function of emotions.
- Session 4: Reducing vulnerability to extreme emotions.
  - Teach students the importance of taking care of their body and its influence on emotional reactivity (ie, balanced eating, adequate sleep, exercise, etc).
- Session 5: Managing emotions or opposite action
  - Teach students how to experience emotions without immediate mood-based action.
  - Teach students how to change or reduce the intensity of their emotions through opposite action.
- Session 6: Distress tolerance or relaxation
  - Teach students strategies to help manage mood during particularly difficult emotional periods (eg, getting bad grade).
  - Teach relaxation training to students to help reduce intense negative emotions.
- Session 7: Perspective taking, problem solving, and pros and cons
  - Teach students how to obtain a more objective assessment of distressing situations.
- Session 8: Relating to others
  - Thinking mistakes.
  - Discuss validation of others and self-validation.
  - Teach students how to best communicate with others, so that can either: (1) maintain relationships and reduce conflict, (2) get what they want or say no, or (3) keep their self-respect.
- Session 9: Review of skills
  - Review skills taught over the course of the program with application exercise.
  - Complete posttreatment survey.

Control: Treatment as Usual

Participants assigned to the control group or treatment as usual are all enrolled in a health education class at their school, which is a state requirement for all high school students. These students will not receive any *Going 4 Goals* programming.

Data Collection Procedures

For the intervention participants, quantitative surveys are completed during the first meeting of the *Going 4 Goals* program as a baseline measure. The surveys are completed again at the end of the ninth session and at 1-, 3-, and 6-month follow-ups. In addition, during the first group session, each participant will set both an academic and personal goal with 3 smaller tasks to reach the goal using the SMART (ie, specific, measurable, attractive, realistic, and timely) framework [35]. These goals are later revisited in sessions 5 and 9, where progress is self-reported. For control participants, the same quantitative surveys are collected in the health education class in the same school that the intervention participants attend using the same timeline (at baseline; approximately 9 weeks after the baseline assessment; and 1-, 3-, and 6-month follow-ups). Control participants will not make SMART goals as part of this study. A snack and pen are given to each participant as an incentive for completing the baseline and posttreatment surveys.

For the follow-up surveys, all participants will receive monetary compensation in the form of gift cards for each completed survey (US $10 for 1 month, US $15 for 3 months, and US $20 for 6 months of follow-up).

Qualitative interviews are also conducted with the intervention participants and school staff either in-person or on the phone approximately 1 month after the intervention to assess the impact of the program, facilitators, and barriers to implementing the intervention. Interviews will be conducted by trained research staff, with steps taken to reduce the likelihood that the group leaders are conducting interviews with students in their own groups. The interviews will last approximately 30 minutes. Youth participants will receive a US $10 gift card for completing the interview, and the school staff will receive a US $25 gift card.

Measures

Quantitative Measures

Demographics

Demographic information is collected during each data collection, starting at baseline. Participants are asked to report their age, gender identity, race, ethnicity, primary spoken language, grade in school, and mental health diagnoses (if any).

Emotion Dysregulation

The Emotion Dysregulation Scale short version [36] is a 12-item instrument used to examine emotional experience, cognition, and behavior. The scale consists of items scored on a 7-point Likert scale ranging from 1 (*not true*) to 7 (*very true*) specific to each aspect of emotional experience (eg, "Emotions overwhelm me"), cognition (eg, "When I'm upset, everything feels like a disaster or crisis"), and behavior (eg, "When my emotions are strong, I often make bad decisions"). The internal consistency has been shown to be high for each subscale (Cronbach α=.93 to .95 [36]).

Impulsivity

The Urgency, Premeditation, Perseverance, Sensation Seeking, Positive Urgency, Impulsive Behavior Scale modified for children [37] is used to assess impulsivity with five 8-item subscales measuring separate impulsivity-related traits: negative urgency, positive urgency, lack of perseverance, lack of premeditation, and sensation seeking. Example items of each scale include negative urgency (eg, "If I feel like doing something, I tend to do it, even if it's bad"), positive urgency (eg, "When I am in a great mood, I tend to do things that could cause me problems"), lack of perseverance (eg, "I finish what I start"), lack of premeditation (eg, "I tend to stop and think before doing things"), and sensation seeking (eg, "I like new, thrilling things to happen"). Participants responded to items on each subscale on a 4-point Likert scale, 1 (*not at all like me*), 2 (*not like me*), 3 (*somewhat like me*), and 4 (*very much like me*), with items coded so that higher scores indicate more impulsive tendencies. Internal consistency has been shown to be high in previous research among youth (Cronbach α=.81 to .90 [37]).

Substance Use

The substance use history measure was adapted from various national studies conducted among youth (eg, Monitoring the Future and Youth Risk Behavior Surveillance System). It consists of 9 items and evaluates substance use in the past 30 days. Participants are asked to indicate how many days they used a substance in the previous month (0, 1-2, 3-5, 6-9, 10-19, 20-29, every day). The substances evaluated are cigarettes (2 items: smoked at all and smoked half a pack or more), smokeless tobacco, alcohol (2 items: had at least 1 drink and had 5 or more drinks in a row), cannabis, inhalants, other drugs (eg, lysergic acid, cocaine, and methylenedioxymethamphetamine), and e-cigarettes.

Distress Tolerance

The Distress Tolerance Scale [38] consists of 15 items that measure self-evaluations and expectations of experiencing negative emotional states. Example items include "My feelings of distress are so intense that they completely take over" and "I'll do anything to avoid feeling distressed or upset." Items are rated on a 5-point scale, 5 (*strongly disagree*), 4 (*mildly disagree*), 3 (*agree and disagree equally*), 2 (*mildly agree*), and 1 (*strongly agree*), with higher scores indicating higher distress tolerance. The Distress Tolerance Scale has been demonstrated to have high internal consistency (Cronbach α=.89 [38]).

Mindfulness

The Philadelphia Mindfulness Scale (PHLMS [39]) is used to measure key constituents of mindfulness: present-moment awareness (eg, "I am aware of what thoughts are passing through my mind") and acceptance (eg, "There are aspects of myself I don't want to think about"). It comprises 20 items rated on a 5-point scale—5 (*very often*), 4 (*often*), 3 (*sometimes*), 2 (*rarely*), and 1 (*never*). Higher scores on the *PHLMSawareness* subscale are associated with higher mindful attention and awareness, whereas higher scores on the *PHLMS acceptance* subscale are associated with less thought suppression and rumination. The PHLMS has shown good internal consistency across clinical and nonclinical samples (Cronbach α=.075 to .91 [39]).

Interpersonal Effectiveness

The Peer Conflict Scale-Youth [40] is used as a proxy for interpersonal effectiveness, as it assesses reactive and proactive aggression. The measure consists of 20 items: 10 items examining proactive aggression, both proactive overt items (eg, "I start fights to get what I want") and proactive relational items (eg, "I gossip about others to become popular"), and 10 items examining reactive overt (eg, "When someone hurts me, I end up getting into a fight") and relational aggression (eg, "If others make me mad, I tell their secrets"). Items are rated on a 4-point Likert scale—0 (*not at all true*), 1 (*somewhat true*), 2 (*very true*), and 3 (*definitely true*). Previous studies have established a high internal consistency (Cronbach α=.93) [41].

Risky Behaviors

The Mood-Based Questionnaire-Children [37] is a self-report measure that assesses lifetime endorsement and the current likelihood of engaging in 24 risky behaviors while being in either an unusually negative mood or an unusually positive mood. Lifetime endorsement is measured on a dichotomous yes

or no scale. The likelihood of engaging in risky behaviors is measured on a 5-point Likert scale, with 1 (*not at all*), 3 (*maybe*), and 5 (*will definitely try*) points. Behaviors assessed on the measure include drinking alcohol, breaking the law, smoking a cigarette or cigar, kissing someone romantically, urinating outside, shoplifting, starting a fight, trespassing, cheating on a test, and disobeying parents. In previous research on adolescents, there has been good evidence of the reliability of the Mood-Based Questionnaire-Children (Cronbach α=.85 to .92 [37]). In this study, 3 modifications were made. First, the mood component was removed from the instructions; thus, the measure assesses the likelihood of engaging in risky behavior regardless of mood state. Second, the timeframe was modified to assess risk taking within the past month rather than lifetime endorsement. Third, an item not included in the original measure was added to assess any cannabis or marijuana use.

SMART Goal Tracking

One of the components of *Going 4 Goals* is creating and tracking SMART goals. Intervention participants are taught that SMART goals should be specific, measurable, attractive, realistic, and timely. Group leaders will assist participants in creating a personal and an academic SMART goal to work on throughout their time in the program, each with 3 smaller tasks that will help them reach their overall goal. Participants then rate themselves on a scale of 1 to 10, indicating their progress toward reaching their goals, with 10 indicating goal attainment. Participants will then re-evaluate their progress in sessions 5 and 9. These goals will not be shared with other participants. Control participants will not set any SMART goals for this study.

Qualitative Measures

Semistructured interviews are conducted with intervention participants and school staff to understand factors related to implementation and program outcomes, including appropriateness for a school-based setting; acceptability by participants; feedback on the logistics and makeup of the group; opinions about group topics, group leaders, and style of delivery; and influence on mental, behavioral health, educational, and social outcomes (Textbox 2). Interviews will be appropriately tailored for each type of interviewee, audiotaped, and last approximately 30 minutes.

Textbox 2. Qualitative interview questions.

Categories and example questions

- *Going 4 Goals* Impact
  - *How did Going 4 Goals impact your day-to-day life?*
  - *How did it impact your relationships parents, peers, and teachers?*
- Process
  - *Tell me about any skills you may have used from the group.*
  - *What did you like most or least about (skills)?*
  - *What were the most or least helpful group activities you participated in?*
- Design
  - *Have you participated in any other groups related to stress management?*
  - *If so, how did it compare to Going 4 Goals?*

Confidentiality

To protect confidentiality, each participant is assigned a subject ID number connected only to their name on a file stored on a secured network and server maintained by the research staff behind a university firewall. The ID number is used for all data collection components (questionnaires, qualitative transcriptions, and goal sheets). All completed informed consent and assent documents are stored in a locked file cabinet inside a locked office. All electronic data (quantitative data files, audio files, and qualitative transcriptions) are also stored on a secured network and server maintained by the research staff behind a university firewall. Contact sheets with participants' email, phone numbers, and addresses, which are used for follow-up interviews and surveys, are stored in a separate locked cabinet inside a locked room. Contact information collected electronically is stored behind a university firewall on a secure, password-protected, restricted-access server.

Intervention participants and their guardians are also assured that student discussions in the *Going 4 Goals* sessions, responses to surveys, and information given during interviews will not be shared with anyone outside of the research team, except for specific circumstances in which the research team needs to breach confidentiality (eg, reports of suicidal or homicidal ideation and child abuse or neglect). Thus, in most circumstances, parents, teachers, or school administrators will not have access to individual responses to the study. When the study results are shared with school administrators, no participant names or ID numbers are included in the aggregate data.

Data Analytic Plan

For the quantitative data, we plan to conduct linear mixed models to examine whether there are significant changes in emotional regulation, distress tolerance, mindfulness, and interpersonal effectiveness skills at the postintervention

assessment compared with baseline in the intervention group. Linear mixed models will also be used to examine significant changes in past 30-day substance use and the likelihood of engaging in substance use and risky health behaviors at the postintervention assessment compared with baseline assessment. We will compare changes in these outcome measures with those of youth in the control group. In addition, as some students may not be present in all sessions, we will test whether there is evidence of a relationship between the number of sessions attended and the outcomes.

For the qualitative data, after interviews are completed, qualitative audio files will be compiled and sent to an external company for transcription. A coding team of 4 research assistants and a project manager will review all transcribed interviews to create coding categories for each question. Student interviews will be split into 2 sections (*impact and skill use* and *logistics*), and administrator and teacher interviews will be coded whole. The team uses Atlas.ti (ATLAS.ti Scientific Software Development GmbH) to create qualitative tables and manually review each transcript to pull relevant quotations from each interview. All coding is also reviewed by another team member for reliability. Finally, qualitative summaries will be created by the coding team and placed in quantitative tables for dissemination.

Results

A university-supported initiative provided funding for this study. Data collection began in July 2018 and was completed December 2021. Participant recruitment began in August 2018. Thirteen groups have been implemented, with 171 participants enrolled in the intervention. In addition, of the 171 participants enrolled in the *Going 4 Goals* program, 146 (85.4%) completed the program, resulting in a retention rate of 85.4%.

The youth participating in the intervention were primarily in the ninth grade (age range 12-16, mean age 14.3 years; SD 3.1 years). The school staff targeted ninth graders to participate in *Going 4 Goals* because of the limited number of mental health and SEL services provided for this age group and difficulties school staff have witnessed with students transitioning to ninth grade (ie, transitioning from middle school to high school amid puberty). Of the 171 youth enrolled in *Going 4 Goals*, most were male (124/171, 72.5%) but diverse in terms of race and ethnicity (61/171, 35.7% Black; 55/171, 32.2% Hispanic or Latino; 42/171, 24.6% White; 3/171, 1.7% Native American or American Indian; and 18/171, 10.5% multiracial). The control group was equally divided by gender (49.4% male), with race and ethnicity mirroring school demographics. Finally, 32.2% (55/171) of the intervention group reported having a mental health diagnosis, compared with 71.3% (122/171) of the control group. Qualitative interviews have also been conducted. To date, 36 students, 7 teachers, and 4 school administrators have completed qualitative interviews. This study is expected to conclude in December 2022.

Discussion

Principal Findings

This paper outlines the background, research design, and intervention components of *Going 4 Goals*, a 9 session DBT-A skill group intervention for at-risk youth implemented in high schools. The proposed study is novel in that there is limited empirical evidence available in the literature on the efficacy of tier 2 SEL interventions for at-risk high school youth, which is critical as such youth are at greater risk for engagement in health-risk behaviors. Thus, receiving appropriate evidence-based services that can reduce such risk is needed. This study aims to fill this important research and clinical knowledge gap.

Implementing the *Going 4 Goals* intervention in high school youth has additional strengths. First, implementing *Going 4 Goals* in schools increases access to mental health services for at-risk youth who may otherwise not have access to such resources. Implementing this program in schools also makes it easier to engage and maintain communication with participants, which can help keep youth engaged and active during the intervention. As mentioned, the participant retention rate has been high at 85.4%. Second, we were able to partner with engaged school administrators who saw the benefits of the program and understood how participants could also enhance their academic performance. Thus, the intervention group is being implemented during the students' homeroom class period. This is done so that there would be minimal disruption to the students' schedules and to ensure that they are still attending their core classes and not missing any foundational curriculum. Holding groups during homeroom also protects teachers' instruction time, minimizing the disruption in scheduling for both teachers and students. Third, given the minimal number of materials needed to implement the program, this is a low-cost intervention, meaning that it can easily be implemented across different school systems and sustained in the long term. Finally, our intervention does not require facilitators to hold special certifications or advanced degrees to deliver the content, meaning that teachers, administrators, and other school staff can administer *Going 4 Goals*. In this study, graduate students serve as group facilitators, with undergraduate students helping as cofacilitators. These students do not have any special certifications or are required to have any specific training other than being trained in the *Going 4 Goals* or DBT-A protocol to lead the groups. A future direction of our work is to train school staff to deliver the intervention, which will establish the feasibility of implementing the intervention by nonresearchers or clinicians.

In addition to the strengths of this intervention, there are also some challenges and lessons learned for future research in this area. First, as we began implementing the intervention, we had some issues with students' punctuality and remembering to attend regularly. To mitigate this, we found that sending reminder text messages the morning of the group, delivering a school-wide announcement over the intercom, and having homeroom teachers remind students individually were effective ways to increase attendance rates. Email reminders were also

sent to students but were not well-received in the age group we serviced. Specifically, students indicated that they do not regularly check their email and thus did not find the email reminders beneficial. Second, scheduling recurring weekly sessions was challenging due to school breaks, state testing, weather delays, field trips, and other unforeseen circumstances. This would, at times, alter our schedule; thus, emphasis on constant communication with schools is crucial. We found that obtaining a finalized semester calendar from the school ahead of time was helpful when working on logistics for the group.

Furthermore, because our research team provides the intervention groups and can only attend at a specified time 1 day per week, any changes or cancelations related to school events meant that we had to completely cancel the session for the week. However, if school staff are trained as facilitators, there will be more flexibility in implementing the intervention, and last-minute school schedule changes will not cause major disruptions in the timeline of the group. Training school staff facilitators will also aid in increasing the access and reach of the intervention to more students and address issues of long-term sustainability in school systems. Third, we found that hosting the groups during school days can be difficult because a designated room is required for the group to meet each week. This issue can also be addressed by training school staff, as they can use their own classrooms or office space for group sessions and have more flexibility in the time of day to hold groups based on room availability. Also related to scheduling was the class period during which the group was held. Generally, groups are conducted during a homeroom or study hall class period to avoid interference with core coursework; however, this may be problematic for schools that do not have a homeroom or study hall period built into their schedules. Therefore, alternative ways to fit the program into school hours may be challenging in other settings.

Future Directions and Dissemination Plans

We anticipate that *Going 4 Goals* will be effective in equipping at-risk students with skills to better cope with stress and reduce their engagement in risky behaviors, such as substance use. Through the completion of qualitative interviews with group participants and school administrators, we will also gain important information on the facilitators, barriers, and attitudinal drivers to enhance tier 2 SEL interventions in high school settings. Such findings will help glean valuable information regarding how best to implement tier 2 SEL and mental health programming to reduce risk taking and increase emotional regulation among at-risk adolescents in high school settings. Future plans include developing procedures to sustain the intervention in schools by training school staff in the intervention protocol and expanding the implementation of the program to other school systems.

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Data Availability

The data generated during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

TZ conceived the study, participated in its design, coordinated writing components, and contributed to the drafting and editing of the manuscript. MW was the project manager of the study and contributed to the drafting and editing of the manuscript; SK, QC, RR, and EFS participated in data collection and contributed to the drafting and editing of the manuscript; MA, MC, MS, and WW participated in the study design.

Conflicts of Interest

None declared.

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Abbreviations

CASEL: Collaborative for Academic, Social, and Emotional Learning
DBT: dialectical behavioral therapy
DBT-A: Dialectical Behavioral Therapy for Adolescents
DBT STEPS-A: DBT Skills in Schools: Skills Training for Emotional Problem Solving for Adolescents
PHLMS: Philadelphia Mindfulness Scale
SEL: social and emotional learning

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Protocol

Developing Reporting Guidelines for Studies of HIV Drug Resistance Prevalence: Protocol for a Mixed Methods Study

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Abstract

Background: HIV drug resistance is a global health problem that limits the effectiveness of antiretroviral therapy. Adequate surveillance of HIV drug resistance is challenged by heterogenous and inadequate data reporting, which compromises the accuracy, interpretation, and usability of prevalence estimates. Previous research has found that the quality of reporting in studies of HIV drug resistance prevalence is low, and thus better guidance is needed to ensure complete and uniform reporting.

Objective: This paper contributes to the process of developing reporting guidelines for prevalence studies of HIV drug resistance by reporting the methodology used in creating a reporting item checklist and generating key insights on items that are important to report.

Methods: We will conduct a sequential explanatory mixed methods study among authors and users of studies of HIV drug resistance. The two-phase design will include a cross-sectional electronic survey (quantitative phase) followed by a focus group discussion (qualitative phase). Survey participants will rate the essentiality of various reporting items. This data will be analyzed using content validity ratios to determine the items that will be retained for focus group discussions. Participants in these discussions will revise the items and any additionally suggested items and settle on a complete reporting item checklist. We will also conduct a thematic analysis of the group discussions to identify emergent themes regarding the agreement process.

Results: As of November 2021, data collection for both phases of the study is complete. In July 2021, 51 participants had provided informed consent and completed the electronic survey. In October 2021, focus group discussions were held. Nine participants in total participated in two virtual focus group discussions. As of May 2022, data are being analyzed.

Conclusions: This study supports the development of a reporting checklist for studies of HIV drug resistance by achieving agreement among experts on what items should be reported in these studies. The results of this work will be refined and elaborated on by a writing committee of HIV drug resistance experts and external reviewers to develop finalized reporting guidelines.

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KEYWORDS

HIV; drug resistance; reporting guideline; prevalence; surveillance; antiretroviral therapy; report; global health; problem; antiretroviral therapy

Introduction

Background

An estimated 38 million people were living with HIV worldwide in 2019 [1]. These large numbers reflect higher longevity in people with HIV due in part to improvements in the management of HIV infection by early detection and early treatment with antiretroviral therapy. One obstacle to the effectiveness of antiretroviral therapy is drug resistance, as it limits the number of effective drugs, increases the potential for onward transmission, and compromises survival [2,3].

Drug resistance to antiretroviral therapy may be acquired when there is viral replication in the presence of a drug [4]. In some individuals, drug-resistant viral strains are already present prior to the start of antiretroviral therapy, referred to as pretreatment drug resistance [5]. This type of resistance can arise due to infection with a drug-resistant viral strain, also referred to as "transmitted drug resistance," or due to prior exposure to antiretroviral treatment (eg, women and children exposed to treatment as part of prevention programs and people who abandoned prior treatments) [6].

HIV drug resistance is a recognized global health problem [7]. People with drug resistance are more likely to experience treatment failure, discontinue treatment, and develop new drug-resistant strains [5]. The rise in drug resistance is one of the greatest threats to global health—without urgent attention, it could result in millions of deaths, an increase in new harder-to-treat strains of HIV, and higher health care costs [8]. The prevalence of HIV drug resistance varies worldwide, and it can be as high as 25% in some countries [9], likely due to the efforts to expand widespread availability of antiretroviral therapy in these settings. Understanding the levels of HIV drug resistance is important to researchers, clinicians, and policy makers because this information can inform guidelines on how treatment should be tailored and what drugs should be used as first-line treatments. For example, in 2020, a total of 21 of the 30 World Health Organization (WHO) drug resistance surveys reported drug resistance to nevirapine or efavirenz in populations initiating first-line antiretroviral therapy above 10% [10].

The prevalence of drug resistance varies among people living with HIV, but is higher in certain high-risk populations such as men who have sex with men, sex workers, transgender people, people who inject drugs, people in prisons, pregnant women, and adolescents and children; resistance prevalence also varies by sex, ethnicity, and HIV subtype due to differences antiretroviral exposures [11-14]. The pooled prevalence estimate of HIV drug resistance is high among men who have sex with men (13.0%, 95% CI 11.0%-14.0%), sex workers (17.0%, 95% CI 6.0%-32.0%), and people in prisons (18.0%, 95% CI 11.0%-25.0%) [15]. Overall, men who have sex with men are more likely to have any drug resistance compared to the general population (odds ratio 1.28, 95% CI 1.13-1.46) [15].

Adequate monitoring of HIV drug resistance across countries and populations is often challenged by heterogenous and inadequate data reporting. In our previous systematic review of pretreatment drug resistance in key populations, we found that the quality of reporting in studies of HIV drug resistance prevalence is low [16]. This compromises the accuracy, interpretation, and usability of prevalence estimates, especially if key data are not reported, including precision of the estimates, representativeness and diversity of the participants included, techniques used to measure resistance, participants' transmission risk group, prior exposure to treatments, and class of drug for which resistance was tested [15]. Our recent methodological study concluded that while reporting has improved over time [8], guidance is needed to ensure complete and uniform reporting to improve the interpretation of study findings, generalizability, and comparability of prevalence estimates, while accounting for differences in geographical settings and populations [17].

In 2010, Moher et al [18] published guidance for researchers seeking to develop health research reporting guidelines, outlining a strategy emphasizing the importance of using robust and widely accepted methodologies. In accordance with this strategy and to initiate the process of developing reporting guidelines for studies of HIV drug resistance prevalence, our prior work evaluated the completeness of reporting of HIV drug resistance prevalence literature, the results of which supported the need for reporting guidelines [15,17]. We have registered this guideline project on the EQUATOR (Enhancing the Quality and Transparency of Health Research) network as CEDRIC-HIV (ChEcklist for studies of Drug ResIstanCe in HIV) [19].

Research Objectives

The objective of this study is to develop a reporting item checklist for prevalence studies of HIV drug resistance by achieving agreement among experts on items that should be reported in studies of HIV drug resistance prevalence. This mixed methods study includes (1) a quantitative phase with survey methodology to identify a list of reporting items considered by participants to be essential, (2) focus group methods to identify emergent themes on reporting items that are essential to HIV drug resistance prevalence studies, and (3) data integration methods to explain discrepancies between quantitative and qualitative data as well as the rationale behind what makes a reporting item important to HIV drug resistance research.

Methods

Design

We will conduct a sequential explanatory mixed methods study (QUAN → qual) among authors of studies of HIV drug resistance. This design comprises two phases: a cross-sectional electronic survey (quantitative phase) and subsequent focus group discussions (qualitative phase). The results of the survey will be used to develop an initial list of potential reporting items and additionally suggested reporting items, which will be evaluated, revised, and expanded upon in the qualitative phase. Transcripts from the focus group discussions will provide key agreement-based insights on why these items are important to report.

Rationale for Design

Mixed methods suit research objectives that cannot met by either qualitative or quantitative methodologies alone [20,21]. The sequential explanatory design is well suited for this research as the quantitative phase provides the recommended reporting items and the qualitative phase provides the rationale for reporting these items. Each of these will inform the guidance and elaboration document that will accompany the checklist.

Sampling

Quantitative Phase

The quantitative phase will include a convenience purposeful sample of corresponding authors of studies of HIV drug resistance. In our 2020 systematic review [16], we searched 10 databases and identified 650 studies of HIV drug resistance. The WHO European region contributed the most studies (34.4%), followed by the Americas (31.7%), Western Pacific (22.0%), and Southeast Asia (6.0%), while African (2.8%) and Eastern Mediterranean regions (1.4%) contributed the fewest studies. We automatically extracted all email addresses (n=160 after deduplication) of the corresponding authors of the included studies. These authors will be contacted by email to participate in the electronic survey. Assuming this is our population of interest, with a 95% CI and a margin of error of 10% and an anticipated survey response proportion of 50%, 84 participants are required. These computations were done with WINPEPI [22]. A sample of n=21 participants will represent ~13% of the target population (N=160), which is sufficiently large to be representative. We intend to recruit as many participants as possible but will use this value to know the minimum required. Study invitations will be sent to all 160 email addresses. If response rates are lower than anticipated, we will use a snowballing approach and invite authors to share the link to the survey with their coauthors. In addition to using social media platforms to disseminate the survey link, HIV journals will also be contacted to share the survey link to authors who have published research on HIV drug resistance in their respective journals.

Qualitative Phase

All survey participants will be asked to indicate if they are interested in the focus group discussions. In the qualitative phase, we intend to include a sample of 20 survey respondents who agreed to participate in the focus group discussion (2 groups of 10 participants). We will select these participants with considerations of sex and geographical diversity, such that we have at least one male and one female participant from as many of the 6 WHO regions as possible: African Region, Region of the Americas, South-East Asia Region, European Region, Eastern Mediterranean Region, and Western Pacific Region [23]. We chose to divide participants into 2 groups of 10 to maximize spontaneity and interaction among participants [18]. In addition, research indicates that groups of at least 6 participants are more reliable while groups greater than 12 are logistically more difficult to coordinate [24,25].

Data Collection

Quantitative Phase

Authors of drug resistance prevalence studies will be invited to take an electronic survey on the Research Electronic Data Capture (REDCap) tool hosted at St. Joseph's Healthcare Hamilton and open from November 2020 to June 2021. REDCap is a secure, web-based application designed for data capture in research [26]. The survey will be pilot tested by the research team prior to launching. Participants will be presented with an overview of the study, its purpose, the investigators, the privacy and confidentiality of their data, and their rights as research participants. They will also be informed on how long the survey will take. Participants will be given the opportunity to provide or refuse consent to participate and the opportunity to withdraw at any time.

The survey includes 23 three-scale ordinal questions, one for each potential reporting item. These 23 items were selected in our previous methodological assessment of reporting completeness of HIV drug resistance prevalence research [17]. This list is not exhaustive, and participants are invited to add more items. Participants will rate whether each item is "essential," "useful but not essential," or "not necessary." Survey items are grouped into four sections in the following order: study-level items, participant items, HIV resistance testing items, and other items. A copy of the electronic survey is provided in Multimedia Appendix 1. This list was generated from a previous systematic review on the global prevalence of HIV in key populations [16]. At the end of each section, participants will be prompted to enter any additional items they believe should be reported, if applicable, into a free-text field. We will also collect basic sociodemographic data such as age, sex, country of residence, profession, number of years as a researcher, and interest in participating in the focus group discussion. Response rates in electronic surveys are often low [27], and thus to maximize responses we will ensure that the email addresses used are up to date, keep the survey as short as possible, declare the estimated time required to complete the survey, and send at least 2 reminder messages [28].

Qualitative Phase

Selected individuals who expressed interest in participating in the survey and who consent to being contacted will be approached to set up a convenient time for a group discussion in October 2021. Participants will be given the opportunity to provide consent prior to discussions and for the discussions to be recorded. Interviews will be conducted over Zoom (a videoconferencing platform with real-time messaging and content sharing). The discussions will be moderated by a chair who will ensure that participants are able to contribute freely and openly. The moderator will introduce the session and initiate the discussions based on a focus group discussion guide (see Multimedia Appendix 2). During the discussions, participants will review the initial list of reported items from the quantitative phase and confirm their choice of whether the items are essential. Participants will also review all additionally suggested reporting items brought up in the survey. Although the focus group discussions are not anonymous, participants will be reassured of the confidentiality of their information and that no

information provided will be traced back to them. The Zoom sessions will be recorded, with the corresponding recordings/transcripts being stored on secure and password-protected servers. The discussions will last about 2 hours. Agreement will be inferred when at least one participant verbally evaluates whether a reporting item is essential or not and there are no verbal objections with the statement.

Data Analyses

Quantitative Phase

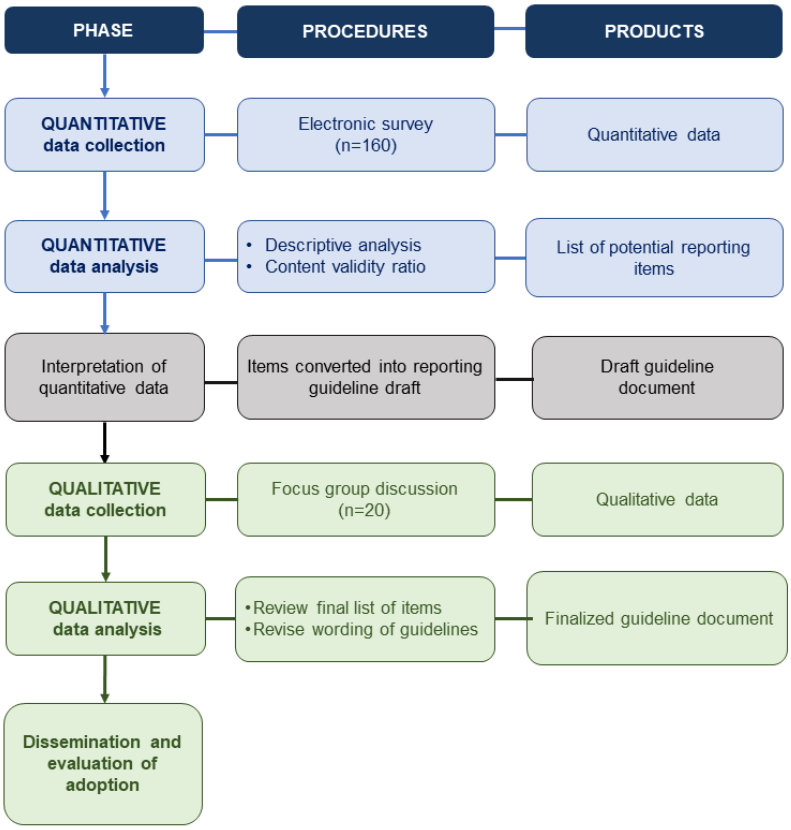
Baseline data and outcomes will be summarized as counts (percentage) for categorical variables, and mean (standard deviation) or median (first quartile, third quartile) for continuous or discrete variables as appropriate depending on the distribution. The ordinal data from potential reporting items will be used to compute a validity ratio. The coding of the essentiality ordinal scale is as follows: essential (3), useful but not essential (2), and not necessary (1). Data on the inclusion of additional reporting items from the open-text fields will be summarized and discussed in the qualitative phase.

A validity ratio will be computed as $VR = [Ne – (N/2)] / (N/2)$, where Ne is the number of participants who indicated that the item was essential (ie, a rating of "3") and N is the total number of participants. This ratio will indicate the items that at least half of the participants consider essential. The validity ratio will be interpreted based on a table of critical values [29]. For example, for 20 participants (N=20), the critical value is 0.500 (ie, at least 15 participants must deem the item to be essential). Only items based on a critical value greater than the set threshold will be considered further [30]. This approach facilitates remote and objective decision-making and the estimation of content validity (the degree to which the items represent the construct of complete reporting). We will use the results of the quantitative data to create a draft list of potential reporting items. This list will only contain reporting items with validity ratios above their critical threshold and will be finalized in the focus group discussions.

Qualitative Phase

The discussions will be transcribed from recordings and coded into categories by two independent coders and compared for consistency. During the discussions, participants will go over the selected set of reported items and confirm their choice of whether they are essential reporting items. They will also examine the grammar and wording of the items. Participants may propose new items (except items dropped from the survey in the quantitative phase) and these will be discussed. These discussions will be used to finalize the selection of items for the finalized reporting guideline. Qualitative data analysis will be informed by grounded theory, where open codes are generated by identifying repetitions in the text [31]. Similar codes will be grouped, with themes emerging from these groupings. Two coders will verify agreement on the generated themes. Disagreement will be resolved by discussion. Thematic analyses will continue cyclically until no new patterns or themes emerge from the data. An outline of the study is shown in Figure 1.

Figure 1. Outline of mixed methods study.



Validation Checks

In the quantitative phase, we will pilot test our survey. In the qualitative phase, we will use member-checking, audio-video recordings, and duplicate coding to validate our data. During the focus group discussions, moderator bias will be minimized by using a discussion guide.

Consensus and Agreement

Consensus will be determined statistically in the quantitative phase using item-specific validity ratios so that the items that at least 50% of participants rated essential are kept in the initial reporting item checklist at the end of the quantitative phase. In the qualitative phase, focus groups will seek agreement on both the reporting item checklist and additionally suggested items generated in the quantitative phase. Agreement is inferred when at least one participant verbally speaks on whether a reporting item was essential or not and there are no verbal objections with the statement. Therefore, agreement also involves the failure to speak up against specific items.

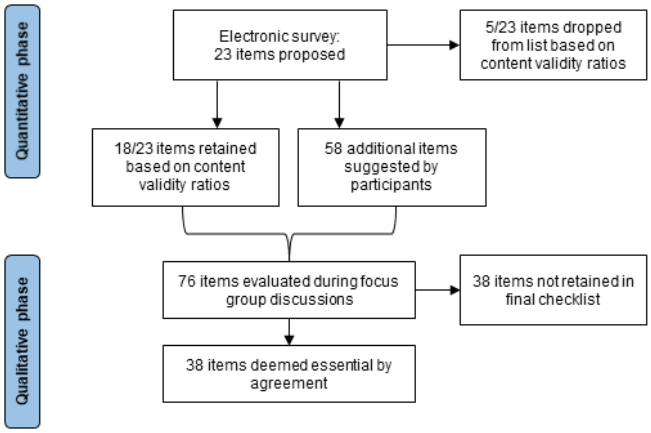
Ethics Approval

This study received ethics approval from the Hamilton Integrated Research Ethics Board (project number #11558) on November 11, 2020, and received annual renewal approval on September 27, 2021. Only participants who provide informed consent will participate in the study. Participants will be able to stop the electronic survey or withdraw from the focus group discussions at any time.

Results

The electronic survey was open from November 2020 to June 2021. In total, 51 participants provided informed consent and completed the electronic survey. Once the quantitative phase data collection and analysis was complete, virtual focus group discussions were held in October 2021. We conducted two focus group sessions of 9 participants in total. As of May 2022, results of both the electronic survey and focus group discussions are being analyzed. A flowchart of items dropped and retained in the checklist is provided in Figure 2.

Figure 2. Flow diagram of reporting items dropped and kept in checklist.



Discussion

Overview

In this study, we will use mixed methods to produce a reporting item checklist of items to be considered in the process of developing reporting guidelines for studies of HIV drug resistance prevalence. We will explore and highlight the insights gained from using mixed methods to meet our study objectives. An explanatory sequential design was selected for this study to allow for the use of qualitative data to explain results from the quantitative findings, and breadth and depth in the data collected [32,33].

We anticipate that most of the initially proposed reporting items presented in the survey will be rated as essential and go on to be evaluated in the focus group discussions. We also expect additional reporting items will be suggested by survey participants, which will also be evaluated in the focus group discussions. During the focus group discussions, we expect considerable agreement on the inclusion of most reporting items proposed in the quantitative phase, with disagreements on areas of wording, grammar, and relevance to specific types of HIV drug resistance research designs. As the purpose of this study is to develop a reporting item checklist and key insights to inform the development of reporting guidelines, we anticipate participants will discuss important considerations that the complete reporting guidelines must consider to be accessible and relevant to all authors and users of HIV drug resistance prevalence research, including any concerns over data privacy and confidentiality.

The strengths of this study include the integration of both quantitative and qualitative methodologies to elicit consensus and agreement from experts on the items that should be reported in studies of HIV drug resistance. Additionally, validation checks will be made in both phases of the study to improve data quality. Study limitations include the susceptibility to low response rates in the quantitative phase and therefore the potential for response bias. We have estimated a sample size to determine the minimum number of responses required for the quantitative phase. However, we have specifically incorporated approaches to enhancing diversity of views by reviewing the geographic coverage of the quantitative data, and purposefully

selecting participants from high- and low-income settings for the focus group discussions and as external reviewers.

Dissemination

The results of this work will be presented as peer-reviewed manuscripts, conference presentations, and as part of a master's thesis. Participants who express interest in the findings of the study will also be sent the results of this work.

Knowledge Translation

We will incorporate several knowledge translation strategies including engagement of opinion leaders in the agreement discussions (eg, study authors), and through linkage and exchange mechanisms (ie, connecting researchers and knowledge users to facilitate dissemination, for example via educational workshops and project summary briefings to stakeholders) [34]. All focus group participants as well as the individuals who have indicated interest in being informed about the outcomes of this research will be engaged as knowledge user partners to help share the reporting guideline. Additional mechanisms will involve academic media releases (eg, St. Joseph's Healthcare Hamilton, public health/HIV societies) and web-based social marketing (eg, Twitter). We will also tailor conference meeting presentations to be educational to inform knowledge users (eg, researchers designing HIV drug resistance prevalence studies) about reporting issues and the current gaps at the design stage of HIV drug resistance prevalence studies, and the need for the reporting guideline.

During focus group discussions, we will ask participants about any perceptions of barriers for practice change (eg, at the level of HIV drug resistance prevalence study design) and uptake of the reporting guideline. We will use this feedback to tailor educational activities (eg, conference presentations) and dissemination efforts (eg, preferences for receiving the information) for this audience. For example, to increase awareness about reporting issues and the reporting guideline, we will present findings about the impacts of missing study data, as well as ensure that we target local, national, and international conferences for dissemination activities. We will publish manuscripts arising from this work in open-access journals.

Knowledge translation impact and evaluation will be measured at the level of the HIV research community using the following metrics: reach and use indicators (eg, number of times manuscripts are accessed and cited), collaboration indicators (eg, endorsement by relevant journals in the field), and practice change indicators (eg, improvements in reporting over time) [35]. For example, indicators of uptake will be measured over time in cross-sectional studies to evaluate changes in reporting practices before and after the publication of the reporting guideline.

Future Directions

The checklist of items and agreement-based insights produced by this study will be refined, elaborated, and considered by a writing committee of experts in HIV drug resistance. We will also invite external reviewers from international organizations such as the WHO, the Joint United Nations Programme on HIV/AIDS (UNAIDS), the Elizabeth Taylor Foundation, and the Centers for Disease Control and Prevention (CDC) to provide feedback on the reporting guidelines.

Conclusions

We seek to develop a reporting item checklist for studies of HIV drug resistance prevalence and a better understanding of what makes a reporting item important to HIV drug resistance prevalence research. The forthcoming reporting item checklist will directly inform the explanation and elaboration document that will have detailed justifications and rationale for each reporting item in the checklist.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Electronic survey distributed as part of the quantitative phase.
[PDF File (Adobe PDF File), 60 KB - resprot_v11i5e35969_app1.pdf]

Multimedia Appendix 2
Qualitative interview guide used during focus group discussions.
[PDF File (Adobe PDF File), 70 KB - resprot_v11i5e35969_app2.pdf]

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Abbreviations

CDC: Centers for Disease Control and Prevention
CEDRIC-HIV: ChEcklist for studies of Drug ResIstanCe in HIV
EQUATOR: Enhancing the Quality and Transparency of Health Research
REDCap: Research Electronic Data Capture
UNAIDS: Joint United Nations Programme on HIV/AIDS
WHO: World Health Organization

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Protocol

Efficacy and Tolerability of Two Novel "Standard of Care" Treatments—Intranasal Esketamine Versus Intravenous Ketamine—for Treatment-Resistant Depression in Naturalistic Clinical Practice: Protocol for a Pilot Observational Study

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Abstract

Background: Intravenous (IV) ketamine and intranasal (IN) esketamine have been studied as novel alternatives to manage treatment-resistant depression (TRD). The objective of this observational pilot study is to compare the real-world effectiveness and tolerability of IV ketamine and IN esketamine in the management of unipolar TRD.

Objective: To compare the effectiveness (primary outcome measure) and tolerability (secondary outcome measure) of racemic ketamine and esketamine in the management of TRD in adults and provide an expert qualitative commentary on the application of IV ketamine and IN esketamine in clinical practice (exploratory objective), focusing on the recruitment process, patient retention, effectiveness, and tolerability of the treatments.

Methods: This is a multicenter prospective observational study of naturalistic clinical practice. We expect to recruit 10 patients per treatment arm—IV ketamine or IN esketamine per center (2 centers, total 40 subjects). Patients experiencing moderate to severe TRD and who are candidates for receiving low-dose IV ketamine treatments or IN esketamine as part of their standard-of-care treatments will be recruited. We will measure the effectiveness of each treatment arm by measuring the severity of depression symptoms using the Montgomery and Åsberg Depression Rating Scale; tolerability, side effects, and the appearance of dissociation symptoms using the simplified 6-item version of the Clinician Administered Dissociative Symptom Scale (CADSS-6); and potential for abuse using a Likeability and Craving Questionnaire. Logistic regression will examine odds ratios, number needed to treat for response and remission, number needed to harm, and likelihood to be helped or harmed of each treatment. Covariate analysis will assess the impact of site and demographic variables on treatment efficacy.

Results: This observational trial was approved by the Queen's University Health Science and Affiliated Teaching Hospital's Research Ethics Board in February 2021. The two research centers involved have started patient recruitment. Our research center (Providence Care Hospital, Kingston, Ontario) has recruited 9 patients so far. We expect to finalize data gathering by August 2022. The manuscript is expected to be published by December 2022.

Conclusions: We hypothesize that both treatments will have comparable rapid and robust antidepressant effects and similar tolerability profiles in a real-world setting for the management of TRD.

International Registered Report Identifier (IRRID): DERR1-10.2196/34711

(JMIR Res Protoc 2022;11(5):e34711) doi:10.2196/34711

KEYWORDS

major depressive disorder; antidepressant; treatment; intervention; pharmacology; pharmacological; Treatment resistant depression; esketamine; ketamine; psychopharmacotherapy; pharmacotherapy; depression; depressive disorder; treatment; observational study

Introduction

Racemic ketamine and its enantiomer esketamine have been studied as novel alternatives for treatment-resistant depression (TRD) in major depressive disorder (MDD) and bipolar depression [1-3]. Studies with intravenous (IV) racemic ketamine have demonstrated rapid and potent reduction of depressive symptoms after the administration of a single subanesthetic dose (response rate=3.01, 95% CI 1.96-4.62; remission rate=3.70, 95% CI 2.28-6.01) [4-8]. Studies with intranasal (IN) esketamine have shown effectiveness in the treatment of TRD for acute and long-term maintenance use (response rate=1.38, 95% CI 1.06-1.79; remission rate=1.47, 95% CI 1.12-1.94) [8,9]. These constitute relevant findings as MDD ranks among the top mental health disorders in the United States and Canada [10-12]. Further, this is the number 1 cause of disability from mental health disorder and number 2 overall, causing substantial losses in quality of life and productivity [11,12]. Unfortunately, most of the published data on the effectiveness and tolerability of these innovative treatments come from clinical trials and not from head-to-head comparative observations of naturalistic clinical practice [8,9,13]. Observational studies are important as they can provide a clearer picture of how these innovative therapies behave in a real-world setting, instead of the more ideal and tightly controlled environment of a clinical trial. Thus, this research study aims to fill this gap, through a head-to-head comparison of IV ketamine to IN esketamine treatment in a Canada-wide multicenter (Providence Care hospital in Kingston, Ontario, and the Canadian Rapid Treatment Center of Excellence in Toronto, Mississauga, and Ottawa) pilot evaluation of naturalistic clinical practice.

Owing to the significant prevalence and overall mental and physical health impact of TRD [14-16], the understanding of the effectiveness and tolerability of IV ketamine and IN esketamine is paramount to the field. Applying meta-analytic comparison across clinical trials, IV ketamine has been shown to be more efficacious and tolerable than IN esketamine for the treatment of depression [8]. Additionally, research has shown that aside from its antidepressant properties, IV ketamine can rapidly reduce suicidal ideation in patients with depression [7,17-20], but IN esketamine has not [21,22]. However, it is important to note that IN esketamine has been approved by the US Food and Drug Administration (FDA) for the treatment of TRD and has clinical trials supporting its use with more long-term data and larger sample sizes than IV ketamine [8]. Moreover, it has been proposed that IN esketamine has a higher affinity for the N-methyl-D-aspartate (NMDA) receptors, is less psychomimetic, and has a greater analgesic and anesthetic effect than the R-ketamine enantiomer. This allows the use of lower doses, potentially with less risk of side effects than IV ketamine [23,24].

Therefore, our primary objective will be to compare the effectiveness of IV ketamine and IN esketamine to each achieve clinical response and remission based on the changes of depression scores according to the Montgomery and Åsberg Depression Rating Scale (MADRS) from baseline to study end point in patients with MDD experiencing TRD. We will use the clinical response to treatment to calculate the number needed to treat (NNT). Our secondary objective will be to evaluate the tolerability of these treatments by systematically assessing the appearance of the most commonly reported adverse effects. We will calculate the number needed to harm (NNH) and the likelihood of being helped or harmed (LHH) [25]. Finally, looking at the recruitment process of patients with MDD experiencing TRD across Canada and the effectiveness and tolerability of these treatments, we will comment on the feasibility of implementing IV ketamine and IN esketamine as standard-of-care treatments as our exploratory outcome objective. The understanding of these novel treatments continues to evolve; thus, our study will supplement the available literature and guide clinical practice in support of either or both treatments in terms of effectiveness and tolerability.

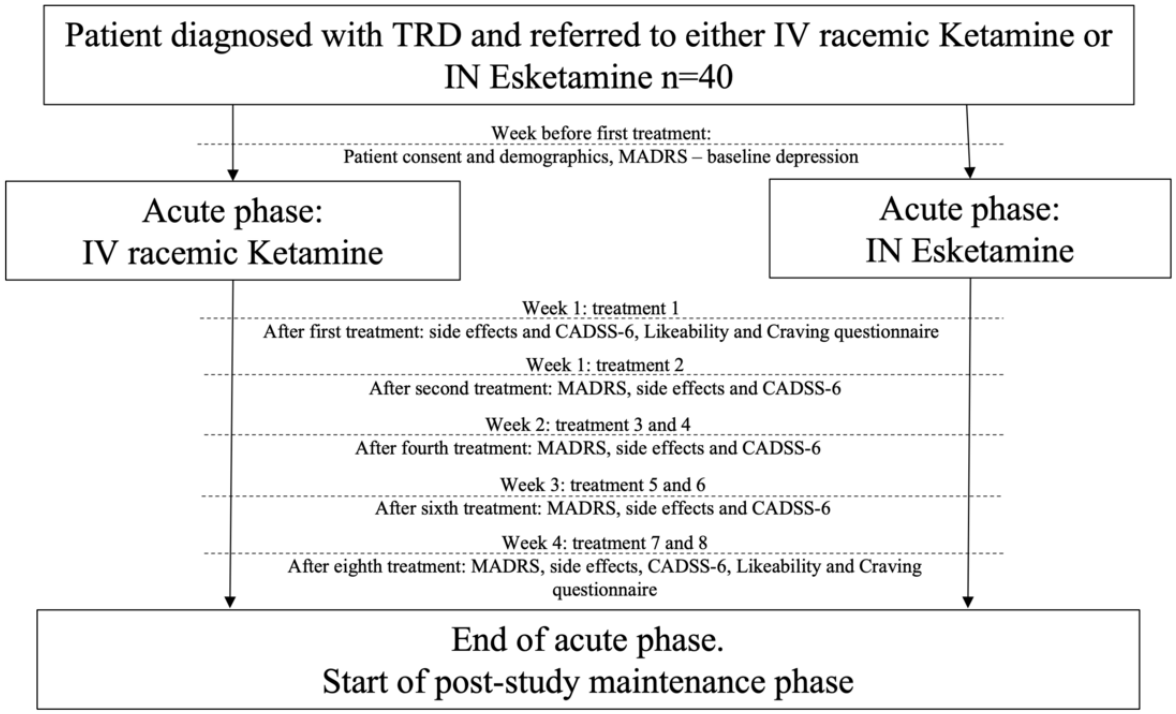
Methods

Study Design

This is a multicenter (Providence Care hospital in Kingston, and the Canadian Rapid Treatment Center of Excellence in Toronto, Mississauga, and Ottawa) observational pilot study of naturalistic clinical practice comparing the efficacy and tolerability of IV ketamine and IN esketamine in the management of patients with MDD and those with TRD [26]. Both IV ketamine and IN esketamine treatments are administered in accordance with the standards-of-care national clinical guidelines [27-29] and pharmaceutical's monograph approved by Health Canada [30], respectively. Participants with moderate to severe MDD experiencing TRD who have been assessed and approved to receive these innovative therapies will go through an acute phase of treatment of up to 8 sessions (IV ketamine or IN esketamine) for 4 weeks. After the acute phase, patients may continue their treatments per each center's clinical protocols and will not be followed as part of this research project. Depression symptom severity will be assessed through the treatment course using the MADRS [31]. Side effects will be recorded through treatment sessions as well, using a checklist of common side effects [32], and we will use the Simplified 6-Item Clinician Administered Dissociative Symptoms Scale (CADSS-6) [33] to assess the severity of dissociative symptoms during treatment (a common side effect in NMDA glutamatergic treatments). Further, potential for abuse of these treatments will be evaluated using a Likeability and Craving Questionnaire

(LCQ) (Dr Jennifer Swainson and Dr Jay Wang, University of Alberta, Edmonton). Figure 1 presents a summary of the experimental design.

Figure 1. Study design overview. This study involves 4 weeks of acute ketamine treatment. During the acute phase the patients will have up to 2 sessions per week. Baseline MADRS total scores will be measured on the week before the first treatment. Then, MADRS, side effects and CADSS6 will be done up to 24 hours after the second, fourth, sixth and eighth sessions (side effects and CADSS-6 done up to 24 hours after the first session too). Likeability and Craving questionnaire will be done up to 24 hours after the first and eighth, sessions. CADSS: Clinician Administered Dissociative Symptom Scale; IN: intranasal; IV: Intravenous; MADRS: Montgomery and Åsberg Depression Rating Scale; TRD: treatment-resistant depression.



Participants and Recruitment

Patients (n=40), aged 18-65 years, with MDD as determined by Diagnostic and Statistical Manual of Mental Disorders, 5th edition, diagnostic criteria and characterized as moderate to severe TRD (baseline MADRS score≥20 and experienced at least 2 failed antidepressant trials of adequate dose and duration [26,34]) will be assessed to receive IV ketamine or IN esketamine treatment as part of their standard-of-care treatment. Exclusion criteria are reporting any active substance abuse, symptoms of psychosis, diagnosis of bipolar disorder, or personality disorder as the primary diagnosis (as defined by the patient's psychiatrist or primary care provider), uncontrolled hypertension, previous negative reaction to racemic ketamine or esketamine, and being currently pregnant or breastfeeding. These patients will be consented to be followed through their treatment course, as part of our research study. This is an observational open-label pilot study, which usually requires a minimum sample of 10-12 participants per treatment arm, considering a main study with a power estimate of 90% and CI of 95% [35-40]. Hence, we consider that our sample size (N=40) is sufficient.

Demographics

After obtaining consent to be enrolled in this study, a demographics questionnaire collecting the following information will be completed: age, gender, marital status, living situation, education, employment, health plan or means of accessing either treatment, drug use, and diagnosed medical or psychiatric comorbidities. The aforementioned factors can influence disease and treatment progression in this patient population [41,42]. For instance, socioeconomic differences could promote or hinder the improvement of depression symptoms because of this treatment. Demographic data will be used to stratify our results to better understand their impact on treatment efficacy.

Rapid-Acting Glutamatergic Treatments

In the clinic, eligible patients will be offered IN esketamine as part of their standard-of-care treatment for TRD initially as an option. If their health insurance coverage cannot cover the costs of IN esketamine, then patients will be offered IV ketamine. We will observe patients undergoing either IV ketamine or IN esketamine treatments and record their vital signs, any potential side effects during and after administration, and changes in severity of depressive symptoms. For the acute phase, both treatments occur up to twice a week over a period of 4 weeks for a total of 6-8 sessions depending on each of the clinical site's protocols. Patients may choose to continue their treatments beyond this point in the maintenance phase, but they will not be followed up as part of this study. Patients are asked to have no solid foods or liquids (nil per os) 2 hours prior to treatment. Treatment sessions will occur at each of the 2 centers as part of their ongoing clinical services.

For IV ketamine, an indwelling catheter placed in the nondominant arm is used. This treatment is administered at a subanesthetic dose: 0.5 mg/kg up to 1 mg/kg (depending on the level of response of the patient to the treatment) over 40 minutes. Administration is carried out with the patient in bed rest, and then the patient is asked to remain in bed for 30 minutes after administration before starting activity as tolerated. Nasal cannula oxygen may be administered if needed using side-stream capnometry monitoring. Pulse, blood pressure, pulse oximetry, and electrocardiography are assessed before the start and through the treatment with IV ketamine. Physiological monitoring data are recorded on a standard anesthesia record beginning 5 minutes before treatment. These patients are discharged after a minimum of 30 minutes post administration, provided that the vital signs have returned to baseline and that the patient is calm, alert, and oriented [27].

IN esketamine is administered as a spray that delivers a 14-mg dose per spray per nostril (28 mg total per device), which the patients self-administer under the supervision of a health care provider. Depending on the response of the patient to the treatment and their clinician's decision, they may self-administer up to 84 mg of IN esketamine, by using up to 3 devices, waiting 5 minutes between each 28-mg dose, per the esketamine product monograph [30]. Patients are allowed to start activity as tolerated after administration. Nasal cannula oxygen may be administered if needed using side-stream capnometry monitoring. Pulse, blood pressure, and pulse oximetry are assessed before the start and for 30 minutes after the IN spray of esketamine. Physiological monitoring data are recorded on a standard anesthesia record beginning 5 minutes before treatment. Then, these patients are discharged after a minimum of 2 hours post administration, provided that the vital signs have returned to baseline and that the patient is calm, alert, and oriented [27].

For IV ketamine, patients will start therapy at 0.5 mg/kg [28,29,43]. If the patient has a partial response (defined as a decrease in the MADRS total score of between 25% and <50% of the baseline) after the second week of treatment, the dose will be increased to 0.75 mg/kg for IV ketamine. For IN esketamine, the recommended dose titration by the manufacturer and approved by Health Canada will be followed (i.e., 56 mg on the first treatment and from then on 84 mg per treatment) [44,45]. Further dose modifications can be carried out on an individual level as needed, and an average dose throughout the treatment will be reported to account for these changes.

Outcome Evaluation

Overview

Effectiveness and tolerability of the ketamine treatments will be determined through assessment scales (MADRS, side effects checklist, CADSS-6, and LCQ) by a trained interviewer, over the phone, through videoconference, or in person when possible. We will inform the patient about the potential risks associated with a phone or videoconference assessment and obtain consent to continue before starting each assessment. Treatment effectiveness will be assessed using the MADRS [31], measuring baseline severity of depressive symptoms the week before the first session of either treatment (IV ketamine or IN esketamine), and then progression of depression symptoms through the treatment course once per week, up to 24 hours after the second, fourth, sixth, and eighth (study end point) sessions. Tolerability will be assessed by tracking the side effects and potential for abuse of either treatment. We used the side effects checklist (Multimedia Appendix 1) [32] and the CADSS-6 for symptoms of dissociation (a common side effect of ketamine treatment) [33] up to 24 hours after the first, second, fourth, sixth, and eighth sessions. Potential for abuse for either treatment will be determined using the LCQ (Multimedia Appendix 2) up to 24 hours after the first and eighth sessions. Figure 1 provides an overview of the study design and the application of each of the mentioned scales through the treatment course.

Primary Outcome Measure

The effectiveness of racemic ketamine and IN esketamine in improving the depression scores will be determined from baseline to the study end point (completion of the treatment course) using the MADRS in patients with an episode of MDD and TRD. Response to treatment will be defined as a minimum reduction of 50% in their baseline depression score. We will calculate the number NNT for response and remission [25] based on this result. Remission from depression is defined as a depression rating of less than or equal to 10 on the MADRS [46]. Improvement in suicidality will be defined as any change in suicidal ideation severity from baseline to study end point using MADRS item 10.

Secondary Outcome Measures

We will determine the tolerability of racemic ketamine and esketamine by calculating the NNH and the LHH [25] based on the number of patients who completed the treatment versus dropouts. Completion of treatment will be defined as the proportion of participants who remained in the study until the completion of the treatment course (6-8 sessions depending on each of the clinical site's protocols). Dropouts will be defined as patients who discontinued the study prematurely owing to any cause and owing to adverse events. Adverse events will be tracked using a checklist of side effects (Multimedia Appendix 1) [32] and dissociation will be assessed using the CADSS-6 [33]. All subjects will complete the LCQ at baseline and the end point to investigate the potential development of craving for these treatments as an adverse event (Multimedia Appendix 2).

Exploratory Outcome Measures

We will gather expert commentary from the attending physicians implementing IV ketamine and IN esketamine treatment at their respective collaborating research centers. We will focus on the recruitment process and overall patient experience (each researcher is asked to keep a systematic record of their recruitment process and patient retention). Then, with this information and the assessment of the effectiveness and tolerability of these treatments, we will make a qualitative commentary on the feasibility of implementing IV ketamine and IN esketamine as standard-of-care treatments in naturalistic clinical practice.

Ethics and Privacy

All components of this study were approved by the Queen's University Health Sciences and Affiliated Teaching Hospitals

Research Ethics Board. To protect their privacy, participants will be given an anonymous and unique code that was used to identify their data through all the assessment measures and data processing and for all purposes of knowledge dissemination (including but not limited to peer-reviewed publications, scientific presentations, grant proposals, and reports). Assessment data will be stored in secured and password-protected laptops for 5 years after the study completion date, and hard copies of consent forms and participants identifying data will be stored on site in secured lockers and destroyed 5 years after study completion. The research team will safeguard the privacy of the participants to the extent permitted by the applicable laws and duty to report. Grounds for breaching confidentiality will include immediate physical risk to the self or others, elder abuse, and child abuse and neglect.

Data Analysis

The collected data will be analyzed by applying descriptive statistics: mean, median, SD, maximum, and minimum scores for primary and secondary outcome measures and patients' demographics data. To assess treatment efficacy, changes in depression symptoms as measured with the MADRS with either IV ketamine or IN esketamine treatment and will be tracked and compared over time (1 month of the acute phase) using within-subjects repeated measures ANOVA for each treatment arm. Further, we will calculate the response to treatment as the proportion of patients who reached a minimum reduction of 50% from their baseline depression score by study end point and the remission from depression as the proportion of patients who reported a MADRS total score equal or less than 10 at the study end point [46]. Logistic regression will be used to calculate odds ratios. Moreover, we will calculate the NNT, the NNH, and the LHH: NNT by considering the response to treatment and NNH by considering the proportion of patients who completed the study versus the dropouts and the adverse effects (side effects checklist and dissociation using the CADSS-6) experienced by the patients. LHH will be calculated as the ratio of NNH and NNT [25]. Linear regression will examine the contribution of treatment arm (IV ketamine versus IN esketamine), site, and patients' demographic data to account for the influence of these variables to our calculation of effectiveness. Adverse events will be reported in terms of frequency through the treatment course. The data will be compared using a Mann-Whitney *U* test to determine if there is a significant difference in the response to the 2 treatments (mean depressive scores, mean dissociation scores, and mean LCQ scores). The effect size of each treatment will be calculated using Cohen *d* [47].

Results

Since this observational trial was approved by the Queen's University Health Science and Affiliated Teaching Hospitals Research Ethics Board in February 2021, we began offering patients the opportunity to participate in this study in March 2021 at the Mood Disorders Services in Providence Care Hospital, Kingston. Thus far, we have recruited 9 patients, and we expect to finalize data gathering from the 2 centers by August 2022 and analyze the findings by October 2022 at which point, we will begin our process of knowledge dissemination (including but not limited to peer-reviewed publications, scientific presentations, grant proposals, and reports). The manuscript is expected to be published by December 2022.

Discussion

Expected Findings

Both IV ketamine and IN esketamine have been shown separately to be effective and potent at managing symptoms of TRD [1-8]. Meta-analytic indirect comparison of these 2 treatments favored IV ketamine, showing that overall, it has a higher response, higher remission rates, and lower dropouts than IN esketamine. Though it is important to mention that phase 3 studies tend to have smaller effect sizes than phase 2 studies [48], and unlike with ketamine, there are phase 3 studies with esketamine, which may impact this analysis [8]. However, IN esketamine has been recently approved for the management of TRD by the FDA and Health Canada [8] and has several features that can make it a more desirable treatment. For instance, its higher affinity for the NMDA receptor means that it can be administered at lower doses than IV ketamine, and IN administration is more convenient and comfortable for patients than IV administration. However, the high cost of IN esketamine treatment may be a significant limiting factor for patients [20,23,49]. Nevertheless, currently, there are no direct comparisons of these 2 treatments in clinical practice, and most of the information that we have about either treatment comes from clinical trials that usually present an overly idealistic version of real-world clinical practice [8,9,13]. Thus, this research study aims to fill this gap through a head-to-head comparison of racemic low-dose IV ketamine with IN esketamine treatment in a multicenter (Providence Care hospital in Kingston and the Canadian Rapid Treatment Center of Excellence in Toronto, Mississauga, and Ottawa) pilot evaluation of naturalistic clinical practice. Hence, through this study, we aim to guide clinical practice in support of either or both treatments in terms of effectiveness and tolerability.

The two main strengths of this study are that it observes the effectiveness and tolerability of these novel treatments in naturalistic clinical practice, and that both treatments are administered in the same 4 clinics and under similar conditions. Naturalistic clinical administration of IV ketamine and IN esketamine would allow us to better understand how these innovative therapies behave in a real-world setting and with the challenges of administering these treatments in clinical practice, such as scheduling conflicts, managing side effects, and modifying dosing schedules in accordance with symptom improvement and side effects, among others. Further, by having both treatments in the same clinical setting, with minimal changes other than the administration route, we hope to minimize external factors that could confound the effect of the treatments.

Our primary outcome focuses on determining the effectiveness of IV ketamine and IN esketamine on symptoms of depression in patients with MDD experiencing TRD. By applying the MADRS [31], we will track the change in the severity of

depressive symptoms and compare the effectiveness of these 2 treatments in terms of clinical response and remission from depression and reduction in suicidal ideation. Clinical response results will be taken into account to calculate the NNT [25] for IV ketamine and IN esketamine. Our secondary outcome focuses on the tolerability of IV ketamine and IN esketamine on patients with MDD experiencing TRD. By applying different measurements focusing on side effects (side effects checklist [32]), including dissociation (CADSS-6 [33]) and potential for abuse or craving (LCQ), we will observe the patients through their treatment course to determine the NNH and the LHH [25]. Our exploratory outcomes will focus on the expert commentary of the attending physicians at each of the collaborating research centers with regard to their recruitment process and patient experience through the treatment course. This information and our assessment of the effectiveness and tolerability of these treatments will be used to make a qualitative commentary on the feasibility of implementing IV ketamine and IN esketamine as standard-of-care treatments in naturalistic clinical practice. From this pilot study, we expect that IN esketamine may be less accessible (owing to cost) and thus less feasible for the average person with TRD. We also expect that both treatments will be similar in terms of effectiveness and tolerability; thus, these results will help inform clinical practice in the use of these novel treatments for the management of TRD.

Limitations and Future Research

The main limitations in this study are associated with the challenges of real-world clinical practice. We foresee that scheduling conflicts with the patients' treatment sessions may cause alterations in the acute regimen, and some patients may choose to stop the treatment abruptly. Further, the significant cost and still scarce insurance coverage for IN esketamine treatment means that only some patients will be able to opt to receive this treatment. As a result, we may have biases in the demographics of patients who are able to receive either treatment—this will be analyzed at the end of the study. Another limitation is that owing to COVID-19 restrictions, we have resorted to carrying out the assessment scales over the phone. This represents an important limitation, as a key part of understanding the patients' mental state is through their body language and their appearance. Furthermore, we are not able to carry out the assessment promptly after the treatment sessions and usually have to wait till the patient gets to their home. This represents a problem, especially for side effect–tracking (including dissociation), as the patient is asked to remember their state several hours after the treatment.

In terms of future direction, as this is a pilot study, we are planning to expand this study to include a comparison with other standard-of-care treatments for MDD and TRD. Further, we are planning to carry out a longer-term follow-up assessment of these patients—for 6 months and 1 year—to further assess the extent of the benefit of these innovative treatments. We will also expand the follow-up assessment to both patients who have continued with routine maintenance and those who have slowly tapered their sessions and may no longer be taking the medication. Through this future study, we could help determine effective ways to apply these treatments in clinical practice to achieve long-lasting results and better understand the potential benefits of these treatments over the long term.

Conclusions

IV ketamine and IN esketamine are novel, rapid-acting, promising treatments for TRD; hence, we aim to understand whether these treatments are comparable in terms of effectiveness and tolerability in naturalistic clinical practice. We hypothesize that owing to the chemical similarity of these two compounds, they would have comparable effects; thus, we hope to inform clinical practice in support of either or both treatments.

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Authors' Contributions

GG acquired the data and drafted and critically reviewed the manuscript. JR collaborated in the multicenter study, was the principal investigator at the external site, and critically reviewed the manuscript. EH and GV conceptualized and designed the study and critically reviewed the manuscript. JS collaborated in the multicenter study, was the principal investigator at the external site, designed the assessment scale for Likeability and Craving of Ketamine/Esketamine, and critically reviewed the study.

Conflicts of Interest

GV has received consulting and speaking honoraria from AbbVie, Allergan, CANMAT, Elea/Phoenix, Eurofarma, Gador, Janssen, Lundbeck, NeonMind Biosciences, Tecnofarma, Raffo, Otsuka, Psicofarma, and Sunovion, and research grants from CAN-BIND, CIHR, PCH and Queen's University. JR has received research grant support from the Canadian Institute of Health Research (CIHR), Physician Services Inc (PSI) Foundation, Labatt Brain Health Network, Brain and Cognition Discovery Foundation (BCDF), Canadian Cancer Society, Canadian Psychiatric Association, Academic Scholars Award, American Psychiatric Association, American Society of Psychopharmacology, University of Toronto, University Health Network Centre for Mental Health, Joseph M. West Family Memorial Fund and Timeposters Fellowship and industry funding for speaker/consultation/research fees from

Janssen, Allergan, Lundbeck, Sunovion and COMPASS. He is the Chief Medical and Scientific Officer of Braxia Scientific and the medical director of Braxia Health (formerly known as Canadian Rapid Treatment Centre of Excellence). JS has received honoraria from AbbVie, Bausch Health, Lundbeck, Otsuka, CCRN, Janssen, Eisai, Sunovion, and is a medical advisor for the Newly Institute. The authors have no further conflicts to declare.

Multimedia Appendix 1
Side Effects Checklist.
[DOCX File , 13 KB - resprot_v11i5e34711_app1.docx]

Multimedia Appendix 2
Likeability & Craving Questionnaire.
[DOCX File , 58 KB - resprot_v11i5e34711_app2.docx]

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Abbreviations

CADSS-6: Simplified 6-Item Clinician Administered Dissociative Symptoms Scale
FDA: US Food and Drug Administration
IN: intranasal
IV: intravenous
LCQ: Likeability and Craving Questionnaire
LHH: likelihood to be helped or harmed
MADRS: Montgomery and Åsberg Depression Rating Scale
MDD: major depressive disorder
NMDA: N-methyl-D-aspartate
NNH: number needed to harm
NNT: number needed to treat
RR: response rate
TRD: treatment resistant depression

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Protocol

Treatment Outcome for Adults in a Residential Program for Binge Eating Spectrum Disorders: Protocol for a Prospective Pragmatic Single-Arm Trial

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Abstract

Background: Most studies reporting treatment outcomes for eating disorders at higher levels of care focus on anorexia nervosa and bulimia nervosa. No studies have been published with a singular focus on examining treatment outcomes for adults receiving residential programming specifically designed for the treatment of binge eating spectrum disorders (BESD), including binge eating disorder and bulimia nervosa.

Objective: The purpose of this paper is to outline the protocol of a prospective study examining treatment outcomes at discharge and 3-month, 6-month, and 12-month postdischarge follow-up, for a sample of consecutive admissions to a residential program specifically for patients with BESD.

Methods: One hundred consecutive admissions to a binge eating treatment program were enrolled in the prospective single-arm trial between January 2019 and February 2020. Data were collected at admission, discharge, and 3, 6, and 12 months postdischarge, with admission, discharge, and 12-month follow-up as the major timepoints of interest. Results across the major timepoints will be analyzed with mixed effects general linear models.

Results: The primary aim is to assess the impact of the program on eating disordered behaviors at discharge and 12-month follow-up, which are hypothesized to improve as a result of treatment. Secondary hypotheses include improvements on comorbid symptoms, including trauma, depression, and obsessive-compulsive symptoms, as well as improvements on medical indicators of health, including cholesterol and triglycerides, at discharge and 12-month follow-up.

Conclusions: This study may aid in the development of treatment guidelines for patients with BESD at higher levels of care and lend support to having specialty treatment programs for patients with BESD.

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KEYWORDS

binge eating spectrum disorders; binge eating disorder; bulimia nervosa; treatment; residential program

Introduction

Background

Binge eating disorder (BED) is defined as recurrent episodes of binge eating in the absence of compensatory behaviors, accompanied by marked distress regarding the binge eating [1]. Lifetime prevalence rates of BED among adults are 0.85%-1.9% [2,3] and are often associated with psychiatric comorbidity, medical complications, and a BMI over 30 [2,4]. Bulimia nervosa (BN) is characterized by episodes of binge eating accompanied by compensatory behaviors such as self-induced vomiting [1]. Outpatient treatment based on cognitive-behavioral therapy (CBT) is generally recommended for binge eating spectrum disorders (BESD) such as BED and BN [5,6]. There are times, however, when patients require higher levels of care, such as residential treatment, to interrupt severe and enduring eating disordered behaviors.

Residential treatment provides 24/7 care focused on psychological/behavioral interventions (as opposed to medical stabilization, which is the focus of inpatient treatment). A systematic review of 19 residential eating disorder treatment programs reported that only 14% of the reviewed studies included patients with BED [7]. In contrast, patients with anorexia nervosa (AN) were included in all 19 studies, and patients with BN were included in 90% of the studies reviewed. It is possible that results for patients with BED have not been reported as frequently as AN or BN due to BED only being a recognized diagnosis since the publication of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) in 2013 [1]. Alternatively, binge eating may be underreported due to its normalization to some degree [8].

One of the few studies reporting results separately for BED was from a residential treatment program for obesity, examining patients with and without BED at 6-month and 5-year follow-up [9]. At both follow-up points, there were no differences in weight loss between obese patients with and without BED. Patients with BED had significantly worse scores on all psychosocial measures at baseline and 6-month follow-up. Another study found significant reductions in weight after a 5-month stay at a residential eating disorder program in Italy [10].

Outcomes for patients with BN are reported more frequently than outcomes for patients with BED, although BN outcomes are often not reported separately from other eating disorder diagnoses, with results reported for the overall sample instead. Residential programs that have reported results separately for patients with BN often find stability in BMI over time and improvements in eating disorder psychopathology and depression [10-14]. Purging behaviors have been shown to decrease almost completely for patients with BN while in residential treatment [15].

Although there are no widely agreed upon essential elements of residential treatment for BED, in their review of residential programs across eating disorder diagnoses, Peckmezian and Paxton [7] found that 52% of programs used CBT as a treatment modality, whereas 33% used dialectical behavior therapy (DBT) and 19% used acceptance and commitment therapy (ACT). Briefly, CBT emphasizes behavioral change and addressing overvaluation of shape and weight [16], DBT focuses on teaching skills such as mindfulness and emotion regulation [17], and ACT encourages patients to develop psychological flexibility and live in accordance with their values and goals [18].

Most residential programs are generally designed for patients across the eating disorders spectrum. No studies have been published with a singular focus on examining treatment outcomes for adults receiving residential programming specifically designed for the treatment of BESD. The purpose of this paper is to describe the detailed protocol of a study prospectively examining treatment outcomes for a sample of consecutive admissions to a residential program specifically for patients with BESD (BED or BN). Patients with AN – binge/purge subtype (AN-BP) were not included in the binge eating disorder treatment program described in this paper, given the need for a different treatment focus for this patient population, including weight restoration.

Primary Hypotheses

It is hypothesized that meaningful improvements (defined here as pre- to posttreatment change with at least a medium Cohen *d* effect size of 0.5) will be demonstrated on measures of eating disorder psychopathology as a result of treatment addressing binge eating and other disordered eating behaviors. It is also hypothesized that a history of trauma and current posttraumatic stress disorder (PTSD) symptoms will moderate treatment effects, in that improvements in eating disorder symptoms will be less marked among those with a history of trauma or current PTSD symptoms. Although some studies have found that PTSD does not result in poorer treatment outcomes for binge eating [19,20], other studies have found that PTSD predicts more binge eating at end of treatment [21] and premature treatment dropout for patients with BN [22]. Given these mixed findings and the assumed increased level of severity in the current population seeking higher level of care treatment, PTSD will be examined as a moderator.

Secondary Hypotheses

It is also hypothesized that meaningful improvements will be demonstrated on a measure of experiential avoidance of weight-related feelings, thoughts, and actions, although no a priori hypotheses are made as to which subscales may improve the most. Depression, dysfunctional attitudes, and quality of life are also expected to meaningfully improve. Small improvements (defined here as pre- to posttreatment change with at least a small Cohen *d* effect size of 0.3) on a measure of obsessive-compulsive symptoms are expected, as addressing obsessive-compulsive symptoms is not a main target for treatment overall in the treatment program, but may be addressed in individual therapy. Anxiety and self-esteem are both hypothesized to meaningfully improve after treatment. Given that the treatment program incorporates trauma-informed care, it is hypothesized that meaningful improvements on a measure of PTSD symptoms will be found. It is also hypothesized that treatment will result in improved levels of triglycerides, high-density lipoprotein (HDL) and low-density lipoprotein

(LDL) cholesterol, and glycated hemoglobin (HbA_{1c}) due to normalization of eating patterns. It is well established that having a BMI over 30 shortens life and adversely impacts years of productive life [23]. The mechanism for those adverse effects is via contributors to the development of the metabolic syndrome and a heightened cardiac risk profile, such as hyperlipidemia and hyperglycemia. Thus, measuring those variables at baseline and then reassessing their serum values after treatment is one way to define the potential value of this program to reduce cardiac risk. Findings from this study may inform treatment guidelines for patients with BESD receiving treatment at higher levels of care.

Methods

Study Design

This study is a prospective pragmatic single-arm trial with consecutive admissions. As with all pragmatic trials, the primary goal of this study was to observe unbiased patient outcomes in a real-world setting. Given the acuity of patients, and the lack of an evidence-based treatment as usual for patients with BESD at this level of care, it was neither feasible nor ethical to execute a randomized or nonrandomized design with a treatment as usual or nontreatment comparison condition. To minimize bias from retrospective reports and convenience samples, this study was devised prospectively to examine outcomes in 100 consecutive admissions who agreed to participate.

Participants and Eligibility Criteria

One hundred consecutive admissions to the Binge Eating Treatment & Recovery (BETR) residential program in a large Midwestern city in the United States who consented to participate were enrolled in this study. The BETR program is part of Eating Recovery Center's (ERC) network of eating disorder treatment programs. ERC is a multisite, national program offering higher levels of care to patients with eating disorders. Treatment is provided by multidisciplinary teams of a physician, licensed psychotherapist, psychiatrist, and registered dietitian, with a focus on evidence-based group therapies. Participants were approached to participate in the study within the first 3 days of their admission date.

Inclusion criteria for patients admitting to the BETR treatment program are the following: (1) age ≥18 years, (2) have binge eating as a predominant symptom associated with their primary or secondary diagnosis at admission, and (3) voluntary consent for treatment from the patient. Patients were recommended for residential level of care (as opposed to partial hospitalization programming) if they had prominent mood and anxiety symptoms (ie, nonsuicidal self-injury, suicidality, sleep disturbance) associated with their eating disorder and/or if they lacked support for recovery in their home environments. Other inclusion criteria included severity of eating disorder symptoms, abnormalities in initial labs, or poorly controlled medical conditions that were exacerbated by eating disorder symptoms (ie, diabetes mellitus), sleep-related disturbances, or nocturnal-related eating. Exclusion criteria that prevented patients from admitting to the BETR treatment program are the following: (1) primary substance use or psychotic disorder, (2) active psychosis, (3) immobility (patients could not be bedbound, and needed to be able to perform activities of daily living independently or with some nursing assistance), (4) high risk for refeeding syndrome or need for refeeding secondary to restriction, due to the lack of capacity for tube feeds/lack of focus on refeeding on the unit, and (5) need for inpatient medical stabilization. Additionally, and without regard to this study, patients are always asked (but never required) to complete a battery of self-report measures at admission and discharge. An additional inclusion criterion for this study was consent to participate in this study in addition to treatment, including providing self-report data and lab draws while in treatment and during follow-up posttreatment. Exclusion criteria for the study were (1) unwillingness to provide informed consent, and (2) the presence of any intellectual disability, cognitive deficit, or physical incapacitation that may have prevented participants from understanding or completing the informed consent process or completing assessment measures.

Study Procedures

In addition to the standard admission and discharge questionnaires, and standard treatment described below, the 100 consecutive admissions for this study were asked to follow additional data collection procedures and were reimbursed accordingly. In addition to admission and discharge questionnaires, patients were asked to complete 6-month and 12-month follow-up self-report questionnaires. Patients were also asked to visit a laboratory facility at 3-month and 6-month follow-up to obtain a blood draw for a lipid panel (total cholesterol, HDL, LDL, triglycerides) and HbA_{1c}. Participants received a US $25 Amazon gift card after completion of each of their admission and discharge assessments, and a US $100 Amazon gift card after the 6-month and 12-month follow-up intervals, for a possible total of US $250 in gift cards for completing all assessments.

Ethics Approval

This study was approved by Salus Institutional Review Board in January 2019 (approval number: ERC-001) and procedures followed were in accordance with the ethical standards of the institutional review board on human experimentation and the Helsinki Declaration of 1975.

Treatment

The BETR program is designed to specifically serve the needs of patients struggling with BESD. A case report suggested that having patients with BESD participate in treatment programs designed primarily for restrictive eating disorders may be problematic due to differing foci of weight restoration versus normalizing eating patterns, as well as patients' comparisons to other patients, which can be detrimental to recovery [24,25]. Although there is little empirical evidence to support this, a study of intensive treatment specifically for patients reporting episodes of overeating (patients with BN, BED, or obesity without binge eating) found improvements in eating disorder psychopathology after 5 weeks, suggesting that targeted specialty care may be more effective and more efficient than general eating disorder treatment programs that address a wide range of symptomatology [26]. In addition, patients with BESD

have unique medical concerns that may best be treated in their own programming. For example, compared to healthy controls, patients with BED have been found to be 13 times more likely to develop type 2 diabetes [27]. They are also more likely to exhibit several other medical complications including insulin resistance, hypertension, acid reflux, and obstructive sleep apnea [4,28-30].

Patients receive personalized treatment from a multidisciplinary team for biweekly individual therapy, biweekly psychiatry visits, weekly family therapy, and weekly dietary sessions. Additionally, patients meet with a primary care physician, certified exercise physiologist, case manager, behavioral health counselors, and nurses upon admission and as needed. The registered dietitian and physician jointly decide on meal plans based on patients' treatment goals and medical conditions. Patients participate in 3 supported meals and 2-3 supported snacks daily. Treatment is focused on regulating eating and treating body image disturbance. The exercise philosophy is on increasing joyful and intuitive movement, increasing mobility when needed, decreasing body shame, and decreasing overexercise or compulsive exercise when present.

In addition to interrupting eating disordered behavior, treatment also focuses on managing comorbid conditions, such as mood and anxiety disorders, and regulating sleep. Patients participate in daily group therapy based on a range of treatment modalities, including enhanced CBT (CBT-E) [16], DBT [17], ACT [18], narrative therapy, and exposure and response prevention, and on a range of topics, including body image, mood and anxiety, and nutrition. A primary focus on CBT-E and DBT was chosen because of the research evidence supporting their use for disorders characterized by binge eating. Trauma-informed care was also part of the treatment program. The average length of stay in the BETR program is 30 days, although this can vary considerably based on patients' progress and insurance coverage.

Measures

Primary Outcomes: Eating Behavior

The Eating Pathology Symptoms Inventory (EPSI) [31] is a 45-item self-report measure of eating pathology with eight subscales: body dissatisfaction, binge eating, cognitive restraint, purging, restricting, excessive exercise, negative attitudes toward obesity, and muscle building. Items are scored on a 5-point scale from 0 (never) to 4 (very often). The EPSI has been shown to have good psychometric properties [32].

The Binge Eating Scale (BES) [33] is a 16-item self-report measure assessing binge eating behaviors that may be indicative of an eating disorder. It measures eating disordered behaviors as well as feelings associated with a binge episode. Items are measured on a 4-point scale, and the measure has been shown to have good psychometric properties [34].

The Night Eating Questionnaire (NEQ) [35] is a 14-item self-report measure of various aspects of night eating, including percentage of food consumed after dinner and frequency of nocturnal awakenings and ingestion of food. Items are scored on a 5-point scale.

Secondary Outcomes: Comorbid Symptoms

The Acceptance and Action Questionnaire for Weight-Related Difficulties – Revised (AAQW-R) [36] is a 10-item self-report measure of experiential avoidance of weight-related feelings, thoughts, and actions with good psychometric properties. It has three subscales: food as control, weight as a barrier to living, and weight stigma [37].

The Eating Disorders Quality of Life (EDQOL) instrument [38] is a 25-item self-report measure assessing the impact of an eating disorder on one's quality of life. It has a total score and four subscales: psychological, physical/cognitive, financial, and work/school. Items are scored on a 5-point scale from 0 (never) to 4 (always). It has been found to have good convergent and discriminant validity and good test-retest reliability [38].

The Beck Depression Inventory-II (BDI-II) [39] is a widely used 21-item self-report measure assessing the severity of depressive symptoms. Items are scored on a 4-point scale, with total scores ranging from 0-63. The measure has been found to have adequate reliability and validity [39].

The Obsessive-Compulsive Inventory – Revised (OCI-R) [40] is an 18-item self-report measure of obsessive-compulsive symptoms. It assesses six groups of symptoms, including washing, checking, ordering, obsessing, hoarding, and neutralizing. Items are scored on a 5-point scale from 0 (not at all) to 4 (extremely). It has been shown to have good internal consistency, test-retest reliability, and convergent and discriminant validity [40].

The State-Trait Anxiety Inventory (STAI) [41] is a 40-item self-report measure of state and trait anxiety, with 20 items assessing how respondents feel "at this moment," and 20 items assessing how respondents "generally feel." Items are scored on a 4-point scale from 1 (not at all/almost never) to 4 (very much so/almost always). Psychometric properties have been found to be adequate [41].

The Rosenberg Self-Esteem Scale (RSE) [42] is a 10-item self-report measure of self-esteem, with items scored on a 4-point scale from 1 (strongly agree) to 4 (strongly disagree). It has been found to have excellent internal consistency and test-retest reliability [42].

The Dysfunctional Attitudes Scale – Short Form (DAS-SF 1) [43] is a 9-item measure assessing dysfunctional attitudes of individuals with depression. Items are scored on a 4-point scale from "totally disagree" to "totally agree." The measure is highly correlated with the original 40-item version of the DAS and has good internal consistency [43].

The PTSD Checklist for DSM-5 (PCL-5) [44] is a 20-item self-report measure that assesses the DSM-5 [1] symptoms of PTSD over the previous month. There are four subscales that correspond to PTSD symptom clusters B (intrusions), C (avoidance), D (negative alterations in cognitions and mood), and E (alterations in arousal and reactivity). It has demonstrated good internal consistency, test-retest reliability, and convergent and discriminant validity among veterans [45]. It has not yet been validated in an eating disorder population. The PCL-5 will be examined as an outcome, but also as a predictor variable to

determine whether patients with higher PCL scores have poorer outcomes compared to those with lower PCL scores.

The Adverse Childhood Experiences Survey (ACES) [46] is a 10-item self-report measure that assesses 10 types of childhood trauma, including physical, verbal, or sexual abuse, physical or emotional neglect, having a parent who struggles with alcoholism, having a mother who is a victim of domestic violence, having a family member in jail, having a family member diagnosed with a mental illness, and having a family member unavailable due to divorce, death, or abandonment. Adverse childhood experiences (ACEs) have been found to be related to a number of psychiatric and medical illnesses in adulthood, often with a dose-response relationship wherein risk for illness in adulthood is related to a greater number of ACEs in childhood [46]. The ACES will be examined primarily as a predictor variable to determine whether patients with more ACEs have poorer outcomes compared to those with fewer or no ACEs.

Secondary Outcomes: Medical/Physiological Variables

At 3 and 6 months postdischarge, patients obtained a blood draw for a lipid panel (total cholesterol, HDL, LDL, triglycerides) and HbA_{1c}. Patients were weighed weekly or twice weekly depending on insurance requirements and symptom presentation (ie, active purging was monitored more frequently with weights and labs). All weight collection was blind. “Blind weighing” involves not sharing weight data with the patient to minimize potential distress that may occur from the patient seeing his or her weight [47]. Table 1 displays a timeline of measures and labs that were collected.

Table 1. Timeline of collection for labs and questionnaires.

	Baseline	Discharge	3-month follow-up	6-month follow-up	12-month follow-up
Labs					
Total cholesterol	x		x	x	
High density lipoprotein	x		x	x	
Low density lipoprotein	x		x	x	
Triglycerides	x		x	x	
Glycated hemoglobin	x		x	x	
Assessments					
Eating Pathology Symptoms Inventory	x	x		x	x
State-Trait Anxiety Inventory	x	x		x	x
Acceptance and Action Questionnaire for Weight-Related Difficulties – Revised	x	x		x	x
Beck Depression Inventory-II	x	x		x	x
Binge Eating Scale	x	x		x	x
Dysfunctional Attitudes Scale – Short Form	x	x		x	x
Eating Disorders Quality of Life	x	x		x	x
Night Eating Questionnaire	x	x		x	x
Obsessive-Compulsive Inventory – Revised	x	x		x	x
PTSD Checklist for DSM-5	x	x		x	x
Rosenberg Self-Esteem Scale	x	x		x	x

A Priori Analytic Plan

All data at admission, discharge, and 3, 6, and 12 months postdischarge will be aggregated for the full sample and examined for patterns of missingness, outliers (>3 standard deviations from mean), and normality of distributions. Our a priori assumptions are that data will be missing at random, and all data will be normally distributed with the appropriately minimal proportion of outlier data points. Mixed models will be used to examine fixed and random effects of linear within-person change in BDI-II, EDQOL, OCI-R, STAI, RSE, DAS-SF, PCL-5, BES, and NEQ across our major timepoints of interest (admission, discharge, and 12-month follow-up). Mixed models will be run both unadjusted, as well as adjusted for person-level variables of BMI at admission, demographic variables of age, race/ethnicity, and gender, and diagnosis. Lastly, to examine the potential for different trajectories within-treatment and posttreatment, nested model comparisons will be conducted comparing the linear mixed models described above with mixed models including a quadratic time variable. Based on an expected effect size of at least d=0.5, and to account for a range of potentially inflated intraclass correlation coefficients that could reduce power, a sample size of 100 was determined to be sufficient to test both the mixed effects main effect hypotheses above, as well as the mixed effects 2-level interactions specified below.

All data at each of these timepoints will also be subset by patients above and below the threshold for history of trauma

(defined as an ACES score ≥4) and above and below the most commonly established threshold for clinically significant levels of PTSD symptoms via the PCL-5 (PCL-5 ≥33) [48]. These subsets of patients will be compared using independent-samples *t* tests to determine any differences in point-prevalence of BDI-II, EDQOL, OCI-R, STAI, RSE, DAS-SF, BES, and NEQ by history of trauma or current trauma symptoms, and traditional moderation analyses with interaction terms added to the mixed models described above to determine any differences in changes over time of BDI-II, EDQOL, OCI-R, STAI, RSE, DAS-SF, BES, and NEQ by history of trauma or current trauma symptoms.

Results

Recruitment of participants began in January 2019 and ended in February 2020. Data collection was completed in May 2021. Data analysis is expected to begin in April 2022, and results are expected to be published in fall 2022. The study was internally funded by ERC.

Discussion

Principal Findings

The treatment program described in this study is unique in that it is developed specifically for, and solely treats, patients with BESD at the residential level of care. It is expected that this program, tailored to the needs of patients with BESD, will result in improvement in eating disorder psychopathology, comorbid mood and anxiety symptoms, quality of life, and improvement in physiological measures of health as a result of changes in eating disordered behaviors.

Several practical challenges in evaluating real-world treatment make it important to develop a protocol and explicitly state a priori intentions and expectations. First, the lack of a control group makes it difficult to assess a program's effectiveness. Nevertheless, our a priori hypotheses on the *degree* of improvement may help findings from this study aid in the development of treatment guidelines for other programs seeking to help adults with BESD, which is critically important given the increased prevalence of BESD compared to other eating disorders, and the medical complications unique to BED [30]. Second, because treatment is not conditional on consenting to provide research data, potential bias from evaluating a program based solely on voluntarily collected research data over time may occur. To mitigate this bias in this study, we prospectively created a protocol that would allow for consecutive admissions to the program to be evaluated without the need for an additional research overlay that may lead to missing data in a biased fashion. Finally, because this is the first study to examine treatment for BESD at a higher level of care, it is important to clarify ahead of time exactly what treatment is being performed, what patients are admitted to the program, and what outcomes are expected as a result of treatment in the program.

Conclusions

This study may aid in the development of treatment guidelines for patients with BESD at higher levels of care and lend support to having specialty treatment programs for patients with BESD. Further, it may aid in improving insurance coverage for BESD, which tends to be less favorable than that for patients with AN or BN who are in treatment at ERC. Future studies should further examine components of treatment programs to determine which elements are most critical to recovery.

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Conflicts of Interest

RDR receives consulting fees from the Training Institute for Child and Adolescent Eating Disorders LLC and receives royalties from Routledge. DLG receives royalties from Guilford Press and Routledge, is Co-Director of the Training Institute for Child and Adolescent Eating Disorders LLC, and is a member of Equip Health Clinical Advisory Board. DVB consults for Eating Recovery Center. All other authors declare no conflicts of interest.

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Abbreviations

AAQW-R: Acceptance and Action Questionnaire for Weight-Related Difficulties – Revised
ACE: adverse childhood experience
ACES: Adverse Childhood Experiences Survey

ACT: acceptance and commitment therapy
AN: anorexia nervosa
AN-BP: anorexia nervosa – binge/purge subtype
BDI-II: Beck Depression Inventory-II
BED: binge eating disorder
BES: Binge Eating Scale
BESD: binge eating spectrum disorders
BETR: Binge Eating Treatment & Recovery
BN: bulimia nervosa
CBT: cognitive-behavioral therapy
CBT-E: enhanced cognitive-behavioral therapy
DAS-SF 1: Dysfunctional Attitudes Scale – Short Form
DBT: dialectical behavior therapy
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EDQOL: Eating Disorders Quality of Life
EPSI: Eating Pathology Symptoms Inventory
ERC: Eating Recovery Center
HbA_{1c}: glycated hemoglobin
HDL: high density lipoprotein
LDL: low density lipoprotein
NEQ: Night Eating Questionnaire
OCI-R: Obsessive-Compulsive Inventory – Revised
PCL-5: PTSD Checklist for DSM-5
PTSD: posttraumatic stress disorder
RSE: Rosenberg Self-Esteem Scale
STAI: State-Trait Anxiety Inventory

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Protocol

Misinformation in Italian Online Mental Health Communities During the COVID-19 Pandemic: Protocol for a Content Analysis Study

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Abstract

Background: Social media platforms are widely used by people suffering from mental illnesses to cope with their conditions. One modality of coping with these conditions is navigating online communities where people can receive emotional support and informational advice. Benefits have been documented in terms of impact on health outcomes. However, the pitfalls are still unknown, as not all content is necessarily helpful or correct. Furthermore, the advent of the COVID-19 pandemic and related problems, such as worsening mental health symptoms, the dissemination of conspiracy narratives, and medical distrust, may have impacted these online communities. The situation in Italy is of particular interest, being the first Western country to experience a nationwide lockdown. Particularly during this challenging time, the beneficial role of community moderators with professional mental health expertise needs to be investigated in terms of uncovering misleading information and regulating communities.

Objective: The aim of the proposed study is to investigate the potentially harmful content found in online communities for mental health symptoms in the Italian language. Besides descriptive information about the content that posts and comments address, this study aims to analyze the content from two viewpoints. The first one compares expert-led and peer-led communities, focusing on differences in misinformation. The second one unravels the impact of the COVID-19 pandemic, not by merely investigating differences in topics but also by investigating the needs expressed by community members.

Methods: A codebook for the content analysis of Facebook communities has been developed, and a content analysis will be conducted on bundles of posts. Among 14 Facebook groups that were interested in participating in this study, two groups were selected for analysis: one was being moderated by a health professional (n=12,058 members) and one was led by peers (n=5598 members). Utterances from 3 consecutive calendar years will be studied by comparing the months from before the pandemic, the months during the height of the pandemic, and the months during the postpandemic phase (2019-2021). This method permits the identification of different types of misinformation and the context in which they emerge. Ethical approval was obtained by the Università della Svizzera italiana ethics committee.

Results: The usability of the codebook was demonstrated with a pretest. Subsequently, 144 threads (1534 utterances) were coded by the two coders. Intercoder reliability was calculated on 293 units (19.10% of the total sample; Krippendorff α=.94, range .72-1). Aside from a few analyses comparing bundles, individual utterances will constitute the unit of analysis in most cases.

Conclusions: This content analysis will identify deleterious content found in online mental health support groups, the potential role of moderators in uncovering misleading information, and the impact of COVID-19 on the content.

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KEYWORDS

online communities; social media; mental health; misinformation; COVID-19; empowerment; content analysis

Introduction

Online Communities for Mental Health Symptoms

In an online community, members can post their thoughts regarding a health condition or personal problems for other members to read and comment on. A support group communication episode is structured hierarchically, beginning with a person's need for information or help (ie, locutor), to which any other member of the group may respond. Regarding the term *comment*, we also say post, utterance, or locution [1]. The reactions to a comment, if there are a fair number, would look like a branch of a tree split into ever more twigs. We refer to the whole branch as a bundle or a thread.

Some questions arising from this are evident: What are the influencing factors in the development of mental conditions? How do posts indicate changes in prognoses? But there are also other questions: Do posters stray? That is, do they prioritize other illnesses above or below their mental condition?

For instance, one of the key results in Cavazos-Rehg et al's [2] study of Twitter was that depression and related factors were the subjects that drew the most attention by a large margin.

Declarative and Procedural Knowledge

An origin or first post typically poses a question addressed to somebody's declarative or procedural knowledge. Briefly speaking, declarative knowledge is a type of knowledge that can be verbalized and, on that basis, taught. Procedural knowledge is a person's experience of how something is working [3]. Another typical demand in a first post would be for emotional support [4]. Griffiths et al [5] proclaimed to have captured the process rather than the end state of seeking support. Successful online support groups were also written about in scholarly journals, contributing to the impression that mental health support groups are an asset to a health care system [6,7].

State of Health

In online communities for mental health symptoms (OCMHs), posts to groups and related comments have been deemed to sometimes have beneficial health consequences. Facebook-based social support, for example, was found to affect general health, mental illness, and well-being [4,8,9].

Regarding online communities, Nimrod [9] stated the following:

> *Findings indicated that online depression communities serve as a sphere for knowledge exchange, sharing the experience of living with depression, and getting inspiration for coping. Involvement in these communities seems to inspire and empower participants by enhancing a better understanding of their condition and encouraging them to fight depression. Therefore, it is suggested that the communities can complement formal care.*

Employing qualitative methods, Takahashi et al [10] found both better and worse states among the members of depression help groups. The authors especially highlighted the possibility of a downward spiral of a worsening state among groups.

Correctness of Information

Deceptive or erroneous, rather than soothing or enlightening, information is also feared [11]. OCMHs may contain messages that contradict medical advice or reinforce unhealthy behaviors, such as those seen in Gavin and colleagues' study [12], where anorexia and the misuse of diabetes medication to lower body weight were advocated on a webpage. The presence of misinformation was previously demonstrated in the context of antidepressant use on Instagram [13].

In a study of 6.5 million interactions generated by 500 posts, phatic posts constituted the strongest predictor of interactions, followed by posts with a positive emotional valence. Half of the posts were about social relations, and more than one-quarter (28%) consisted of health misinformation [14]. The article by Beck et al [15] reported on a content analysis that revealed emotional support to be the most frequently sought type of support and, at the same time, a majority of messages related to task rather than relation. Rueger and colleagues [16] reported that advice is more often followed when advice seekers perceive more similarities between themselves and advice givers (see Sillence [17]). The classical term for this is selective perception. If the perception of similarities between advice seekers and givers exerted some influence on advice acceptance, an adaptation by seekers regarding the type of internet service they chose was not observed [18].

A controversial subject is the correctness of internet content. However, recent articles posit the internet's capacity to work against misinformation [19]. It is, however, unlikely that everyone who comes into contact with the misinformation will also be made aware of the correction. Different tensions may arise when the recognition of the increasing role of social media in health information consumption leads to the choice of traditional (ie, nonsocial) media for research [20].

The consequences of taking part in online communities can be differentiated into communicative and medical. Communicative consequences include ease of access to knowledge, enabling contact, or helping to find other people in a similar situation. These consequences are often considered the primary effects, as in a systematic review study by Moorhead et al [21]. The research methods in this area cross over into language use and mood analysis [22,23]. Medical consequences are the health effects, which are considered the secondary effects. One of the most engaging content analyses of online depression communities [9] summarized the influences of participation in terms of ameliorating the understanding of participants' conditions and encouraging them to fight depression.

Professional Moderation as an Uncovering Strategy

OCMHs can be moderated by health professionals; for instance, a health professional could prevent detrimental activity by establishing behavioral- and content-related rules and could moderate threads (eg, there could be restrictions on the mention of drugs and related matters). Moreover, they could censure or remove individuals from the OCMH [5]. Health professionals are defined in this study as people with a documented academic or professional background in the health field, but not restricted

to mental health. These include psychiatrists or psychologists as well as nurses and general practitioners.

Very few studies have been conducted concerning the role of moderators and administrators (admins) in countering misinformation. Recent studies on moderation have shown that this type of intervention could improve the quality of online discourse (eg, Wadden et al [24]). However, these studies did not specifically investigate the impact of misinformation and its uncovering.

Online Communities in the Midst of a Pandemic

Italy was the first Western country to experience a nationwide lockdown and this changed health priorities, with public health authorities advising the public to limit the use of health services [25]. Psychiatric emergency department admissions and referrals, in fact, diminished [26,27]. According to recent literature, this has led to the transition of many aspects of pre–COVID-19 life to a web-based format [28].

Although many studies focused on addressing the impact of social media during the pandemic (eg, the impact on panic [29] or on educating the public on prevention measures [30]), the reverse has not yet been investigated. A few studies have examined the characteristics of informational support or public sentiment related to COVID-19 (eg, Boon-Itt and Skunkan [31]), but a broader view on the impact on mental health conversations is still lacking. To the best of our knowledge, no study has been conducted to investigate whether people with mental health disorders turned more often to OCMHs or whether they gained or lost trust in the official health care system and encountered a higher amount of erroneous information.

An interesting question that arises is whether social media subjects changed as a response to the pandemic situation and whether the management of people's mental conditions adjusted to the challenging situation.

Only one study investigated whether social media use increased after the onset of the COVID-19 pandemic; however, the community that was investigated did not specifically include people suffering from mental health disorders [32].

Objectives and State of Knowledge

In this paper, we seek to describe how posts to OCMHs and their comments can form deceptive or erroneous information in terms of false declarative or procedural knowledge, wrong judgments, and motivations for detrimental decisions.

Furthermore, an exploratory research question asks whether misleading content would be distributed unequally at the different stages of illness trajectory. It is hypothesized that advice seeking or giving related to treatment, versus diagnosis or symptoms, will have the highest prevalence of misinformation.

Our study aims to do the following:

1. Add information about the influence of professional moderation on mental health communities to the knowledge base.
2. Demonstrate whether and how communication in mental health communities changes as a result of the COVID-19 pandemic.
3. Analyze the first two study aims for their role in misinformation and its detection.
4. Attempt to compare declarative and procedural knowledge demands.

This could be read as the foundation of a study that will test a complex causal model with demanding contemporary statistics, such as structural equation modeling. Instead, the method that will be used is a quantitative longitudinal content analysis [33]; 3 years of posts on a Facebook health community page will be analyzed, including some background and interpretive links.

Methods

Aspects of Content Analysis

Content analysis is a method to identify, record, and aggregate predefined elements of communication content [33,34]. The method assumes that the vast biological, educational, and social differences among the coders will not lead to a completely different understanding of similar text or other material. Selective perception has to be downgraded to the degree that different coders with different experience are able to understand and record communication content reliably. This is achieved by coder training and a collection of rules to understand and record the content; the rules are referred to as the codebook (Multimedia Appendix 1). The study will use utterances from Facebook OCMHs as the sampling frame. Facebook was chosen for several reasons: it is the largest social media company, it has a large presence of support groups, and it allows for easy retrieval and monitoring of member discussions, together with the number of threads present, compared to other types of OCMHs, such as blogs and forums.

Ethics Approval

The guidelines outlined in previous social media research informed this study's procedures [35]. Permission to conduct research was requested from admins or moderators of private and public Facebook groups. A group privacy setting of "private" means that while anyone can see the group, approval by an admin or another member is required to join; the content on a group's wall is only visible to members [36]. In public groups, any Facebook user can join the group (ie, no admin permission is required).

Furthermore, regarding data that will be reported in scientific publications, we will remove any real names or other personal information, as well as usernames, that could potentially result in a breach of anonymity and privacy that would reveal any information that could be attributed to a single individual (eg, photographs and locations) [37]. In addition, researchers abstained from any communication or interaction with the individuals in the groups. Ethics approval was obtained by the ethics committee of the Università della Svizzera italiana on April 19, 2021 (CE 2021-4).

Codebook Development

The first draft of the codebook was developed based on the categories identified in previously published works, for example, with respect to the distinction between information seeking and giving versus emotional support (eg, Greene et al [38] and Lerman et al [39]). However, in the later stages of codebook development, an inductive approach was applied as potential themes arose from the reading of data [40].

The second step in developing these coding schemes involved applying the codebook to a sample of Facebook threads in online support groups. This was done in an iterative process. This coding often resulted in the identification of further coding criteria linked to the variables of interest.

Coder Training

Usually, content analysis coders do not have to have special skills. In this case, however, coders were required to have clinical experience and familiarity with mental conditions, and they were selected accordingly. Two coders were hired; both of them are psychologists with a background in health communication.

The two coders familiarized themselves with the coding procedure, the variables of interest, and the theoretical constructs underlying the codebook (eg, the concept of misinformation and the distinction between procedural and declarative knowledge). The coders were then assigned a number of threads (ie, consecutive posts) to code independently and to find shortcomings in the coding scheme. Codings were discussed among the coders and with the project management team. The iterative testing took place from November 2021 to January 2022.

When disagreement between coders and the management team had dropped to acceptable levels, the coders coded another 60 utterances for a reliability check, calculating a preliminary Krippendorff α. Coding problems and disagreements, as well as shortcomings in the codebook, were discussed, and the instrument was revised once more. In the next step, the two coders coded an additional 11 threads (61 utterances) and calculated the Krippendorff α for each variable coded (see the Results section).

Sampling

Selection of OCMHs

Following a procedure suggested by Birnbaum et al [41], the project manager, in November 2021, searched for Italian-language OCMHs in the then-available versions that were present on Facebook. We chose the Italian language because most people posting in Italian would likely live in places influenced by Italian culture. If we had chosen English, a poster could live virtually anywhere and be subject to all kinds of cultural influences.

The ensuing recruitment process was visible to any member of the online groups found during the search in November 2021. The project manager entered a personal profile that was accessible to other group members. Using the personal profile, she requested to join the group, if private, and wrote a post on the group wall asking to be contacted by an admin or a group moderator. When contacted, she sent the same message to all the group moderators, which contained a brief presentation of the research team, the study aim, and the study methodology. When requests were made for additional information, she called the admins on the phone. In the event of no response, she wrote on the group wall twice and sent up to three reminders (every 2 or 3 days) to all of the group's admins.

The aim was to select the most appropriate groups within the following categories: moderated by health professionals, moderated by peers, group size (ie, number of members), activity (ie, a group was considered active if posting at least 30 posts per month), and whether the group was already active since January 2019.

Selection of Material: Inclusion and Exclusion Criteria

Criteria for Origin Posts and Related Threads

The inclusion criteria for origin posts are follows: request information or advice in a decision situation, include calls for help regarding a health-related matter, or include calls for emotional help [42]. The reason for the restriction to these three types of origin posts was to concentrate as much as possible on real and severe issues. Posts will be also excluded when addressing relational communication among members in the group or when addressing group issues. Posts will be excluded when they appear to advertise professional services. All subsequent reactions to an excluded post will also be excluded. They will also be excluded when a moderator initiates the communication among members in the group or when the post is addressing group issues among members. The project management team will only pass along threads that meet the inclusion criteria and hold back those meeting the exclusion criteria.

Criteria for Posts

The project management team will only pass along posts that meet the inclusion criteria.

Criteria for Comments

Facebook has a nested comment feature that allows users to reply to individual comments on a post, with three maximum layers. In this way, subconversations among particular users can be collapsed and hidden into subthreads nested within a thread. Comments will be included only when posted at the first level; subthreads will not be considered as, according to the literature, they easily present parallel discussions [43]. No exclusion criteria are included for comments (ie, when an utterance is unrelated to the topic of discussion or deals with relational issues, this will be coded accordingly).

Data Management and Coding Analysis

The project manager downloaded the threads and inserted them into a Microsoft Word file that already matched utterances (ie, posts and comments) with the sorting variable's number (ie, the identifier that will be used later in the coding phase). In this step, emojis were replaced with keyboard symbols; see Multimedia Appendix 2 for examples of coding. A Microsoft Excel file was then created with the columns related to the

formal variables (eg, date and the number of total comments in the post) already filled out.

Data were then coded by human coders, who entered their ciphers and letters into a data file in Microsoft Excel. Coders could correct obvious errors in sorting variables. Coders had help filling out the columns through the use of the IF function in Excel (eg, "NA" [not applicable] was automatically inserted for variables of advice giving when the utterance was coded as advice seeking).

After coding was complete, the data were transferred into the data matrix of a statistics program (SPSS); data cleaning was performed to make sure that there were no undefined codes in the file and that subgroup analyses were based on the correct filters and showed a reasonable number of posts or utterances. Generally speaking, content analysis can be based on counting different units. We will distinguish the individual utterances at a detailed level, which will make up the data matrix.

Variables were coded on the locutor level and for all utterances, meaning that they do not form their own level. Every utterance has exactly one locutor. When a new utterance is added, a new coding line is opened, and the new utterance is coded in the new line under the given thread or within the same bundle. When the data file is cleaned, different entries for the same locutor are taken together.

Variables

Overview

The codebook contains three types of variables: formal, locutor, and content variables; see Multimedia Appendix 1 for a complete list of the variables and coding details and Multimedia Appendix 3 for a summary.

Formal Variables

The bundle and sorting variables (V1 and V2) have the technical function of distinguishing comments from different threads and monitoring the related timeline of comments. V3 codes the number of total comments in the thread. V4 (ie, locution date) is coded based on the first utterance in the thread. To allow for comparisons between the times after the COVID-19 pandemic had hit and before, the study precisely records the date of publication. That allows for recoding of dates into any period one could wish for. V5 codes for reactions, such as likes or loves; this can be coded for all utterances (Multimedia Appendix 2).

Locutor Variables

The locutor variables include locutor ID (V6), to track interventions within and between threads, and locutor gender (V7). Locutor status (V8) was coded for every utterance, though the status will likely be the same in all utterances for one locutor within a bundle. However, change will not be ruled out, and one and the same locutor can have different statuses across bundles and within bundles. Furthermore, the medical-scientific qualification of the locutor (V9) will be coded if mentioned anywhere in the locution.

Content Variables

Overview

These variables were coded at the comment level. V10 has the purpose of distinguishing when the locutor is seeking or giving advice. A code of "seeking" represents the seeking of advice, information, decision help, or emotional help. Requesting one of the types of support often includes, implicitly or explicitly, the admission of one's limited abilities or energy, of failure, or of weakness. The origin utterance should, as a rule, be coded as seeking, also due to the inclusion criteria. The categories include the following: declarative knowledge question (ie, know that), procedural knowledge question (ie, know how), asking for help in making a health decision, and asking for emotional support. Later, other members of the support group may join in making the same or other requests. A code of "giving" means that the locutor did, or tried to do, what was requested. First, the success or failure of the locutor is not of import to the coding. To code an utterance as a reaction, an explicit link must be there. In this variable, a value of 0, which represents that neither giving nor seeking was indicated, aims to facilitate coding for utterances that do not indicate advice seeking or giving (eg, problems within the Facebook group, greetings, or requests for further information).

There will be a filter here, with posts coded as 0 stopping the coding, those coded as seeking being directed to V11 (ie, motivation for a seeking locution), and those coded as giving being directed to V12 (ie, action through a giving locution). The categories are as follows: answer to a declarative knowledge question, answer to a procedural knowledge question, call to action, and providing emotional support.

In summary, we can connect the content variables that are especially important for this study as follows:

- Variables regarding the effects of the pandemic: V11 to V13
- Variables regarding the role of the professional: V16 and 17
- True and false variables: V14 to V19
- Declarative and procedural variables.

For V11, we code what the origin post or any other locutor actually wants, if seeking. This is done with four rather broad and abstract categories; this is the basis of a fundamental division we have drawn. The categories are as follows: an answer to a declarative knowledge question (ie, know that), an answer to a procedural knowledge question (ie, know how), asking for or giving help in making a health decision, and asking for or giving emotional support. For V12, we also code the answer of a responding group member in terms of declarative knowledge (ie, the locutor provides declarative knowledge to the recipient), procedural knowledge, call to action (ie, the locutor makes a referral to a health professional), and emotional support.

The type-of-illness variable (V13) is coded in the following way. The utterance is coded for the disease it relates to; up to three diseases can be coded. This can be identified more explicitly (ie, direct mention of the illness) or implicitly (ie, through drugs mentioned). The treatment options variable (V14)

indicates which treatment options are communicated in an utterance. It is possible to code more than one treatment option; medication types will be identified through Multimedia Appendix 4. This variable contains 16 categories grouped as follows: hospitalization, psychotherapy, medication, surgical interventions, and alternative interventions. The treatment evaluation variable (V15, a-c) indicates how the locutor evaluates the treatment (a) together with the presence of the mention of (b) adverse effects and (c) treatment interruption. When a locutor suggests a treatment, this is coded as if the treatment is evaluated positively.

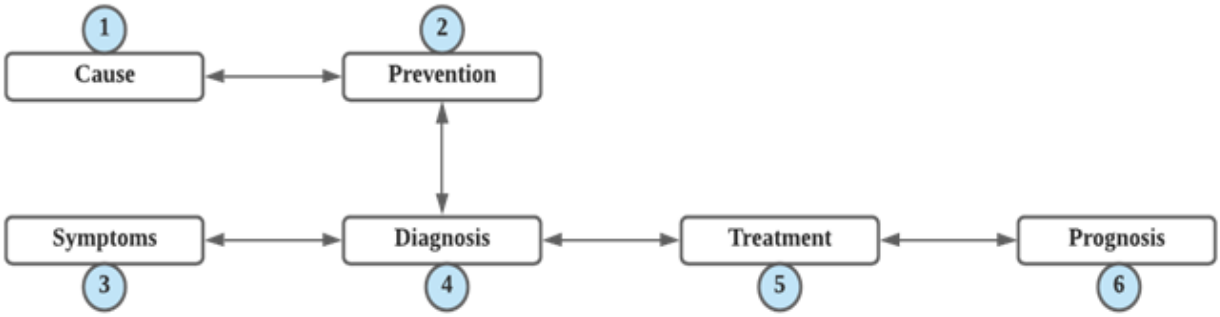
Furthermore, V16 (a-c) investigates (a) whether a health professional is mentioned, (b) the related sentiment *toward* the health professional, and (c) the doctor-patient relationship. Notably, two mental health professional types—psychologist and psychotherapist—will be coded in the same category (value of 1), because when pilot-testing the codebook, users in online support groups rarely distinguished correctly between the two.

Furthermore, the argument quality used by the advice giver is coded in V17. The categories are as follows: empirical knowledge, professional knowledge, secondhand professional knowledge, secondhand unprofessional knowledge, direct anecdotal evidence, or indirect anecdotal evidence.

Misinformation will be investigated in V18. Misinformation is defined as "cases in which people's beliefs about factual matters are not supported by clear evidence and expert opinion" [44]. Misinformation will be categorized into content-related and context-related types. Content-related misinformation refers to situations in which the utterance does not present evidence in support of other claims that used poor-quality evidence or no clinical evidence to support them. On the other hand, context-related misinformation refers to when, irrespective of the quality of the information communicated, the information is not adequate for the context as (1) the locutor does not hold all the knowledge necessary to justify their comment or (2) the locutor does not have the status to be able to make certain inferences. Furthermore, a category specific to misinformation in advice seeking was added to classify when the locutor asks for help while basing the request on wrong assumptions (eg, "antidepressants don't work for me, can you recommend a natural method?"). A category (ie, specifier) was added for utterances containing incorrect terminology, such as stigmatizing or inappropriate terms. Furthermore, misinformation correction will be also measured dichotomously. Misinformation correction will be considered not only as "the presentation of information designed to rebut an inaccurate claim or a misperception" [45], but also when a locutor simply expresses disagreement with a previous misinforming utterance.

V19 is dedicated to the investigation of the illness trajectory and aims to identify at which stage the advice seeker needs informational or emotional help. This does not identify the stage at which the locutor is at the moment, but the stage at which the request can be collocated. Illness trajectories include the normal course of events and developments that span from either the patient or a physician noticing something is wrong up to successful or failed treatment. The trajectory standardizes what people think or say about illness and, thus, enables quantitative coding. It consists of six cornerstones: (1) causes and risk factors, (2) prevention, (3) symptoms of mental conditions, (4) diagnoses that support-seekers converse about, (5) treatment, and (6) prognosis. These six cornerstones describe and structure the illness trajectory. The pairwise combination of two cornerstones creates a theme, for instance, which symptoms indicate which diagnosis. In Figure 1, the boxes represent the cornerstones and the arrows represent the themes (ie, pairwise beliefs); some themes can be constituted by cornerstones that are not next to each other. We turn to the cornerstones first, followed by the themes.

Figure 1. Illness trajectory. The boxes represent the cornerstones and the arrows represent the themes.



Causes and Risk Factors Cornerstone

Causes necessarily come at the early stage of the trajectory. When the disease moves into a patient's focus, the disease's causes are no longer as interesting as they would have been, had a patient been aware of what condition they would develop. This appears in the trajectory as prevention.

Prevention Cornerstone

If causes are known or assumed, a rational decision can be made of what could be done; for instance, if it is known or believed that lack of exercise causes coronary disease, a patient would have to exercise more to protect themself from this condition.

Symptoms Cornerstone

Receiving information about newly noticed or, in fact, new symptoms is expected to be a frequent subject on support websites and a frequent motive for posting an origin locution. Attention to and worry about symptoms will be linkable to diagnosis. The corresponding locutions are statements regarding which symptoms point to which diseases. An example would be “Sudden loss of body weight without a change in diet or an uptake of exercise is often a sign of depression.”

Diagnosis Cornerstone

This cornerstone represents the diagnosis or condition that is discussed in the utterance, not a diagnosis that anyone in the support group might or might not have. Categories of diseases were taken from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). The structure of the conditions were also taken from the DSM-5, which enables coding of an imprecise use of language.

Treatment Cornerstone

Treatment decisions, in reality, often have several criteria to consider and weigh against one another. All of the utterance categories are, of course, situation specific. Therefore, the recommended treatment may not be specific and, in discussions, it may often be reduced to either psychotherapy or medication.

Prognosis Cornerstone

This cornerstone encompasses the prospect of recovery along with adverse effects and medication interruption. An adverse effect is an undesired harmful effect resulting from a medication or other intervention.

Themes

Themes were then identified as entities that are defined as pairs of cornerstones, such as “causes and risk factors in relationship with symptoms” or “symptoms in relationship with diagnosis.”

Results

Codebook Development

We first demonstrated the usability of the proposed systematic framework with 11 threads (61 utterances) coded independently by two coders. The KALPHA macro for SPSS for Windows (version 26; IBM Corp) [46] was used to calculate the Krippendorff α; the coders reached intercoder reliability (α=.89, range .73-1). Then, 1534 units of analysis (144 threads) from two Facebook groups were retrieved and analyzed by two coders. Intercoder reliability was calculated on 293 units (19.10% of the total sample; Krippendorff α=.94, range .72-1).

The α values were calculated for the following: locutor gender (α=1), locutor status (α=1), medical-scientific qualification of locutor (α=1), seeking versus giving advice (α=1), motivation for seeking advice (α=.93), action through giving locution (α=.95), type of illness (α=.95), treatment options (α=.98), treatment evaluation (α=.93), adverse effects of treatment (α=.93), treatment interruption (α=.94), health professional mentioned (α=.97), sentiment toward health professional (α=.72), doctor-patient relationship (α=.95), argument quality (α=.93), misinformation (α=.90), misinformation correction (α=.91), and illness trajectory and themes (α=.98).

Content Analysis

In total, we have contacted 21 groups; five groups were public but were still asked for approval. Of these groups, 14 agreed to participate in the study. Among those who agreed to participate, according to the selection criteria, we chose two groups: one moderated by a health professional (n=12,058 members) and the other led by peers (n=5598). Information on the number of participants was retrieved in November 2021.

Analytic procedures will be determined in detail. In addition to descriptive statistics of the variables considered, the analysis will combine different units of analysis levels (eg, utterances in relationship to threads). The independent variables will be recoded from the locutor variables and the locutor role of seeking advice versus giving advice: put simply, the seeking of posters, their qualifications, and the illnesses by which they are afflicted. Interfering variables will be the seeking and giving dichotomy, the type of illness, the treatment mentioned, the sentiment toward the health professional, and the argument quality. Misinformation and misinformation correction will be the principal dependent variables.

The study will contribute to investigating potential detrimental effects, and possible mitigating factors, of OCMHs.

Discussion

Expected Findings

Findings will be explained by the concepts of health literacy and health empowerment. In the context of the two concepts, certain communication elements of health subjects are associated with erroneous utterances. Working with the two concepts presents the problem of a striking plurality of concepts as well as operationalization. We, therefore, will not link measures or data, but will look at the origin of erroneous health beliefs and detrimental decisions and will provide the link by way of interpretation.

Consequently, health literacy and empowerment were not coded anywhere in this content analysis. In spite of this, some understanding of the theories behind data collection might help us understand what is being measured and why. Therefore, a few more words on health literacy and empowerment are added here. Health literacy can be defined as the “capacity of individuals to obtain, process, and understand the basic information and services needed to make appropriate health decisions” [47]. Knowledge is not mentioned but is identified in the same writing as a moderator of health literacy. It is certainly a product of literacy and a facilitator of further knowledge acquisition [48]. This position of knowledge and health literacy gives us reason to consider the discussion, application, and evaluation of knowledge as major elements of erroneous consequences of health literacy.

Empowerment, in general, was defined as regaining mastery of one’s life [49]. That concise formulation can be specifically applied to health empowerment, which would be limited to matters of health, including prevention, care, disease, and

treatment. Empowerment becomes harmful when thinking about and discussing competence in making medical decisions. Competence has the same meaning as in legal provisions or social norms: granting the *power* to make decisions. Competence in another sense refers to the *ability* to make decisions. That sense of the term belongs to health literacy rather than empowerment. Expressed in modal verbs, competence regarding legal and social norms that is related to empowerment is about what you *may* (ie, are allowed to) do; the other sense is related to health literacy and is about what you *can* (ie, are able to) do. Agreeing to nonprofessional decision-making (ie, supporting a patient in the belief that he does not need to seek medical consultation) belongs here. Keeping a patient away from a doctor when he or she should see one is the second element of deleterious consequences, this one resulting from an overestimation of empowerment. An example is the linkage between empowerment and using internet health services [50].

Aside from a few analyses that will compare distinct threads, individual utterances will constitute the unit of analysis in most cases [51]. More specifically, we expect misinformation to be more prevalent at specific stages of the illness trajectory, such as the treatment stage, and that professionally moderated OCMHs will present a lower number of misleading messages or negative comments toward health professionals and treatment options.

Furthermore, in addition to COVID-19 impacting the subjects of discussion, we expect the highest amount of misinformation to occur during the pandemic year 2020.

Strengths and Limitations

To our knowledge, this is the first piece of research that will examine OCMHs using the methodology of longitudinal quantitative content analysis. The study will permit us to overcome the limitations of automatic text analysis. However, limitations should be taken into consideration, for instance, female and male genders cannot always be reliably inferred from names, and this categorization limits the variety of gender identities.

Future Directions

We are not yet aware about the impact of OCMH messages on members' intentions and behaviors in terms of professional help seeking or attitudes toward health professionals and treatment options. Future research may wish to explore this aspect.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Codebook.
[DOCX File , 52 KB - resprot_v11i5e35347_app1.docx]

Multimedia Appendix 2
Reactions and emojis.
[DOCX File , 65 KB - resprot_v11i5e35347_app2.docx]

Multimedia Appendix 3
Summary of variables.
[DOCX File , 30 KB - resprot_v11i5e35347_app3.docx]

Multimedia Appendix 4
Medication types.
[DOCX File , 30 KB - resprot_v11i5e35347_app4.docx]

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Abbreviations

admin: administrator
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
OCMH: online community for mental health symptoms
V: variable (when used with a number)

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Protocol

Development of an Internet of Things Technology Platform (the NEX System) to Support Older Adults to Live Independently: Protocol for a Development and Usability Study

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Abstract

Background: In a rapidly aging population, new and efficient ways of providing health and social support to older adults are required that not only preserve independence but also maintain quality of life and safety.

Objective: The NEX project aims to develop an integrated Internet of Things system coupled with artificial intelligence to offer unobtrusive health and wellness monitoring to support older adults living independently in their home environment. The primary objective of this study is to develop and evaluate the technical performance and user acceptability of *the NEX system*. The secondary objective is to apply machine learning algorithms to the data collected via the NEX system to identify and eventually predict changes in the routines of older adults in their own home environment.

Methods: The NEX project commenced in December 2019 and is expected to be completed by August 2022. Mixed methods research (web-based surveys and focus groups) was conducted with 426 participants, including older adults (aged ≥60 years), family caregivers, health care professionals, and home care workers, to inform the development of the NEX system (phase 1). The primary outcome will be evaluated in 2 successive trials (the Friendly trial [phase 2] and the Action Research Cycle trial [phase 3]). The secondary objective will be explored in the Action Research Cycle trial (phase 3). For the Friendly trial, 7 older adult participants aged ≥60 years and living alone in their own homes for a 10-week period were enrolled. A total of 30 older adult participants aged ≥60 years and living alone in their own homes will be recruited for a 10-week data collection period (phase 3).

Results: Phase 1 of the project (n=426) was completed in December 2020, and phase 2 (n=7 participants for a 10-week pilot study) was completed in September 2021. The expected completion date for the third project phase (30 participants for the 10-week usability study) is June 2022.

Conclusions: The NEX project has considered the specific everyday needs of older adults and other stakeholders, which have contributed to the design of the integrated system. The innovation of the NEX system lies in the use of Internet of Things technologies and artificial intelligence to identify and predict changes in the routines of older adults. The findings of this project

will contribute to the eHealth research agenda, focusing on the improvement of health care provision and patient support in home and community environments.

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KEYWORDS

independent living; older adults; Internet of Things; wearable electronic devices; activities of daily living; mobile phone

Introduction

Background

Globally, the population is aging. In Ireland, population estimates for 2021 revealed that adults aged ≥65 years accounted for 14.8% of the total population [1], and this percentage is expected to nearly double by 2051 [1]. In Ireland, we observed an increase in life expectancy, which surpassed the European Union average in 2017 because of significant reductions in major causes of death such as circulatory system diseases and cancer [2]. One of the challenges is that those who live longer do so with a combination of chronic disease, multi-morbidity, and frailty. Support for independent living is, therefore, a major concern for older adults themselves, in addition to family caregivers and health and social care providers. As the vast majority (95%) of older adults in Ireland live in private households [3] and want to remain living at home, this is primarily a community-based issue requiring a home-based response.

Connected health and remote health care are seen as key drivers of home-based health and social care delivery. The use of these technologies has the potential to sustain and accelerate improvements in quality of life and health, and enhance the independence of an aging population [4]. The emergence of new *smart home* and Internet of Things (IoT) technologies have the potential to integrate information technology with assistive technologies highlighting potential for ambient-assisted living systems. These assisted living systems have the potential to support an aging population to meet their needs with minimal digital literacy required [5]. Ambient-assisted living systems incorporate devices such as wearable and in-situ sensors, voice-controlled systems, and smartphones, all connected to the IoT that can be remotely monitored, controlled, or accessed and provide services that respond to the perceived needs of the users [6]. These devices generate and capture massive streaming data, which contain valuable information that needs to be mined to facilitate timely actions and better decision-making [7]. Machine learning and big data analytics will undoubtedly play a critical role in enabling the delivery of future smart care services. Machine learning and big data analytics have been investigated to facilitate the automatic recognition of activities of daily living (ADL) in older adult populations [8,9], which is an important component in the understanding of quality of life and health and well-being. Other data analytics approaches have focused on using periodicity intensity to identify deviations in day-to-day activity patterns in older adults [10].

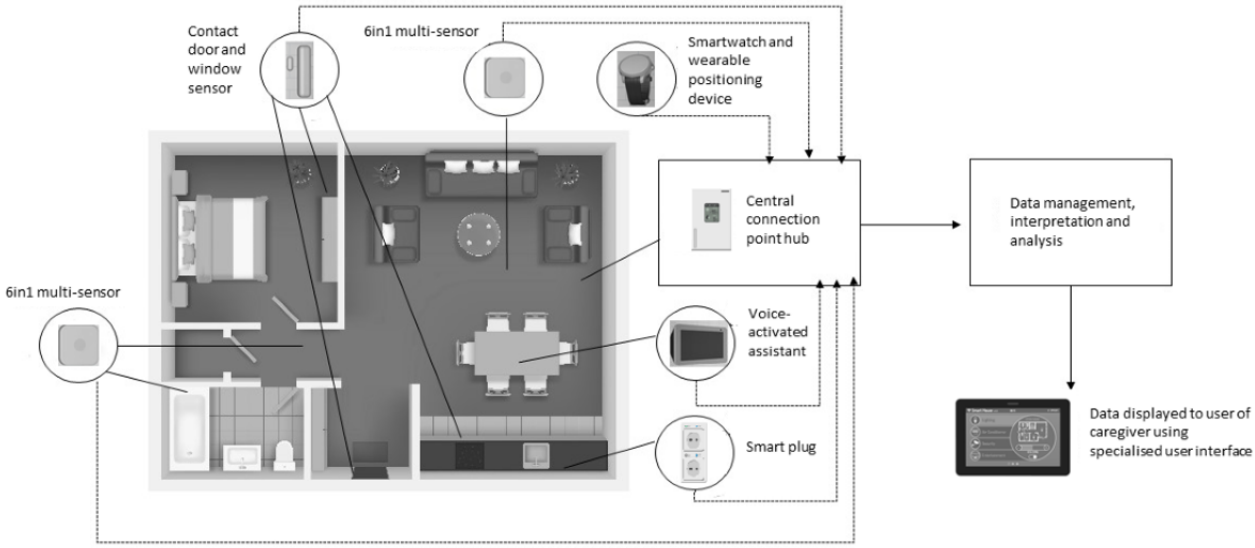
Efforts to support independent living using IoT and wearable technologies among older adults have been investigated for a range of purposes, including physiological monitoring, for example, monitoring health status [11] notifying health care providers of changes in health status [12]; emergency detection and response, for example, falls detection [13]; safety monitoring and assistance, for example, reminding and prompting older people to take medication, which in turn supports independence and safety [14]; personal assistance, for example, automating daily tasks and home maintenance [15]; and social interaction monitoring and assistance, for example, enabling communication and connection with social networks [16]. However, evidence suggests that the use of wearables and IoT technologies to support independent living [5] highlights that a moderate to low usability or user-friendly approach is reported in most of the studies, largely owing to technical issues surrounding the deployment of technologies. Further research focusing on the usability and acceptability of IoT smart home systems in older adults is warranted.

The NEX project is a multidisciplinary research collaboration involving researchers at the Centre for e-Integrated Care, the School of Nursing, Psychotherapy and Community Health, the School of Psychology, the School of Health and Human Performance, and Insight Centre for Data Analytics in Dublin City University (DCU) working with leading Irish technology companies DAVRA and Danalto. This project was funded under the Disruptive Technologies Innovation Fund administered by Enterprise Ireland (grant DT-2018-0258). The overarching aim of the NEX project is to develop a technological solution that will enable older adults to remain living independently at home for longer periods and facilitate caregivers to care for their family members or clients or patients in a nonintrusive manner.

The unobtrusive nature of the NEX system is critical to ensure that participants being monitored barely notice the existence of the sensing device or procedure, and therefore, are prone to less bias and burden. Codesign approaches with relevant stakeholders (described in phase 1) inform the design of the NEX system. The final NEX system design consists of a range of IoT technologies, including a smartwatch (measurement of sleep and step count), voice-activated assistant (entertainment and reminder functionality), contact sensors (detect activity around the home and opening and closing of doors and cupboards), smart plugs (measure energy use of appliances), motion sensors (detect movement, temperature, humidity, and light in the home), positioning wearable device (developed by industry partner Danalto to distinguish the activity of the user in multi-occupancy households), hub (central connection point for sensor devices), tablet (display NEX system data to participants), and a cloud-hosted secure device management (developed by the industry partner DAVRA), as shown in Figure 1. Innovation in the NEX system is underpinned by the use of a variety of

IoT technologies in conjunction with artificial intelligence to develop an integrated system that can detect changes in the usual routine (periodicity and ADL detection). The data generated from the IoT devices will be used to drive the automatic detection of ADLs that are presented back to caregivers and participants. The rules for detecting these ADLs will, in turn, be automatically created using the well-known a priori algorithm for mining association rules [17]. In addition, a positioning device for the purpose of personalizing activities within the home (will assign an action; eg, use of a door or an ambient value such as motion to a specific individual within a household) is being developed as part of this project to support the integrated system.

Figure 1. The NEX system.



The data generated from the NEX system may objectively depict aspects of health and behavior affected by age-related changes, and the data generated from this system could serve as an insightful resource when making health-related decisions. For example, sedentary lifestyle is a well-known age-related change prevalent among many older adults and has been associated with adverse health [18]. Previous studies have highlighted that, in some cases, self-report activity data do not accurately reflect actual activity levels [19] and therefore have limited use in providing insights required to make positive changes. The NEX system, which incorporates wearable sensors and other types of sensing devices with advanced data analytics, has the potential to objectively identify ADLs and provide a detailed analysis of users' activity levels and lifestyles. This in turn would allow older adults to view their data and identify the specific context of how sedentary behaviors occur (eg, reading a book and using a computer). The NEX system data can be used to consider adaptive strategies; for example, the use of timely reminders to promote physical activity. By having access to their detailed health data and behavioral patterns, older adults can make timely adjustments in health behaviors themselves or present the data to health care providers and family caregivers to develop personalized adaptive strategies together. Equally, the impact of these strategies or interventions can be objectively monitored in the home environment, thus providing feedback to older adults and care providers on outcomes.

Objective

The project was structured in 3 phases to achieve the overall project aim. Phase 1 aims to work with stakeholder groups (older adults, health care professionals, family caregivers, and homecare support workers) to identify user needs and requirements to inform the NEX system design using mixed methods research. Phase 2 aims to investigate the technical performance and understand the participant engagement of the NEX system as a pilot testing phase for a duration of 10 weeks. Phase 3 of the project will commence in January 2022, and will incorporate the findings from phase 2 to inform the refined NEX system design. This phase will focus on a larger-scale, real-world deployment of the NEX system (n=30 older adults aged ≥60 years) being tested in the homes of participants for a minimum of 12 weeks. At the end of the 12-week period, participants can decide whether they would like to use the NEX system for a further period. A longer timespan is needed for the trial in phase 3 so that the periodicity of habits associated with normal living can be established. In addition to investigating the technical performance of the system in real-world deployment, a key research objective of phase 3 is to develop an automated approach to identify ADL unique to each participant. This study aims to describe the 3 phases of the overall NEX project.

Methods

Phase I: User Needs Requirements

Study Overview

Despite mounting evidence of the role of technology in supporting older adults to live independently at home [5,20,21], it is critically important that any proposed technology be aligned with core requirements. This underpins the objective of this phase: to provide user needs and requirements to ensure the

development of systems that blend user needs with technological advancements. A user-centered design approach [22] was used to identify user needs and requirements. This codesign approach focused on partnering with end users to design the NEX system technology. The aim of the codesign workshops was for older adult participants and other stakeholder groups (family caregivers, home support workers, and health care professionals) to play an active role in the exploration of their needs and the possibilities that technology can bring to their lives.

Participants

Stakeholder recruitment took place in January 2020, and initial codesign face-to-face workshops commenced in March 2020. The COVID-19 pandemic and subsequent restrictions on movement resulted in a change in methodology to facilitate data collection during this period. To develop the project plan, the research team designed and deployed a web-based survey in June 2020 and conducted web-based workshops from August to October 2020. In all, a total of 4 stakeholder groups were recruited for the user needs requirements (UNR) aligning with the target population; these included older adults, family caregivers, home support workers and health care professionals. Overall, 426 stakeholders participated in the face-to-face workshops, web-based surveys, and web-based workshops. Older adult stakeholders were the largest participant group (265/426, 62.2%), followed by family caregivers (83/426, 19.5%), health care professionals (51/426, 12%), and home care support workers (27/426, 6.3%).

Procedures

Using a user-centered participatory codesign methodology, face-to-face workshops were conducted, including the use of personas designed to be fictitious but authentic end users. Participants assisted in developing scenarios around the persona that captured a particular issue, where technology could enhance self-management competencies or provide the support needed. A total of 2 workshops involving 17 participants (15 older adults and 2 family caregivers) were completed in March 2020 before the introduction of the first set of restrictions associated with COVID-19.

The onset of the COVID-19 pandemic resulted in an adjustment to our methodology, including a web-based survey and web-based workshops. The overall aim of the web-based survey was to gain insights from the 4 key stakeholder groups to examine how technology might play a greater role in supporting older adults to live independently at home to assist in the development of the NEX system. One overarching survey was designed as 4 individual surveys with specific questions tailored to each stakeholder type. One participant classification question assigned each participant to a relevant set of survey questions. In brief, the survey consisted of a mixture of open-ended (free-text response questions) and forced-response single- and multiple-choice option questions.

Following the web-based survey, 13 web-based workshops were conducted to facilitate discussions centered on stakeholders' opinions on how technology can support independent living and to gather user views about specific forms of technology to support independent living for older adults. Specific technology solutions (voice-activated assistant, ambient sensors, wearables, and an integrated system) were demonstrated to the participants via video. Survey responses were exported to SPSS (version 25; IBM Corp), and descriptive statistics and chi-square analyses were applied to examine common attitudes among the respondents. Inductive thematic analysis [23] was performed on free-text responses from the survey and all workshop transcripts.

The research efforts described above highlight several key user requirements, design, and implementation considerations. The research team developed a user needs requirement specification document outlining the UNR, the potential system requirements (the functions of the system must be able to perform), the data requirements (the types of information that a system must be able to process), and other requirements, including user support and training. This enabled the research and technology partners to map user needs to technology solutions while ensuring that the user, system, and data requirements were adhered to.

Phase 2: Friendly Trial

Study Overview

With the UNR study (phase 1) phase of the project, the primary objective of the phase 2—Friendly trial was to investigate the technical performance and participant engagement of the proposed NEX system as a pilot for phase 3. To achieve this, the proposed system was installed in the homes of 7 healthy older adults (aged ≥60 years) for 10 weeks. The proposed NEX system consists of a voice-activated assistant, ambient sensors, and a wearable accelerometer-based device. Consumer devices are used in the NEX system prototype to ensure safety, reliability, and acceptability. An external market analysis was completed, and the devices highlighted in Textbox 1 were selected on the basis that these devices had an excellent connection process, long-lasting battery life, ease of installation, and most importantly, these devices did not require a dedicated router in the participants' homes, which reduced the amount of technology that needed to be installed in the participants' homes. All technology providers were screened by the DAVRA (industry partner) compliance team to ensure that the devices were International Organization for Standardization 27001 certified (an internationally recognized certification of data security) and were compliant with the General Data Protection Regulation and the Health Insurance Portability and Accountability Act. In addition, a Data Protection Impact Assessment was completed by the DCU to ensure the safety and privacy of all the trial participants' data.

Before the Friendly trial, the original plan was to demonstrate and test the system in the DCU community laboratory environment with participants to identify and resolve issues relating to the NEX system, which could be addressed before the technology was installed in participants' homes. However, COVID-19 pandemic restrictions impacted the ability to bring participants into the community laboratory in the DCU and the ability of technicians and researchers to visit participants' homes for installation and training. To overcome these barriers, the Friendly trial was redesigned to involve the self-installation of the NEX system by the participants themselves with remote support. To investigate the feasibility of this self-installation

for the Friendly trial, 2 researchers conducted self-installation with remote support in their own homes. The NEX system was installed at each home for approximately 12 weeks. The NEX system consisted of (Textbox 1) contact sensors on entry and exit doors to home and contact sensors on drawers and cupboards in the kitchen; smart plugs for kitchen appliances; 6-in-1 sensors to detect motion within rooms in the home alongside temperature, humidity, luminescence, UV light, and vibration; a Sony mWatch as an alert system (call for assistance) with GPS tracking and for measurement of sleep duration and step count; and an Amazon Echo Show 8 voice-activated assistant for entertainment and reminder functionality. The researchers' demonstrator efforts highlighted key issues related to greater preconfiguration of the system, more installation and training support, ongoing technology management (eg, charging), and more instruction regarding the removal of the components of the NEX system. It also highlights that the proposed NEX system may be burdensome for self-installation in the target group of older adults. This feedback was communicated to the technology partners and resulted in the production of high-quality installation manuals and videos and a 24-hour technical support helpline to support the Friendly trial self-installation.

Textbox 1. The technology components of the Friendly trial NEX system.

Friendly trial NEX system components

- Sony mWatch
- Amazon Echo show 8
- Samsung SmartThings hub
- Aeotec door and window sensor 6
- Samsung SmartThings smart plugs

Participants

In May 2021, 7 healthy older adult participants were recruited to the NEX Friendly trial, whereby the NEX system was installed by participants themselves in their own homes for a duration of 10 weeks. For the purposes of this research, *healthy older adults* were defined as adults aged ≥60 years living independently with or without one or more stable chronic conditions. Older adults who are currently acutely ill or who meet any of the criteria for *very high risk* with relation to COVID-19 [24], apart from age, were not eligible to take part. The aim of this study is to investigate the performance and participant engagement of the potential components of the *NEX system*. Participants (N=7) ranged from 63 to 87 years of age; 5 (71%) participants were women, and the remaining 2 (29%) were men. All participants were living alone in urban areas of Ireland (6 living in Dublin [urban] and 1 living in a rural location outside Dublin). Although most participants (6/7, 86%) described their health as "very good" or "excellent," 86% (6/7) of participants reported having one or more chronic illness and 44% (3/7) of participants noted that physical modifications were made to their home to assist with access. All participants had a home broadband connection, reported regular use of a smartphone, indicated some level of familiarity with technology, and were willing to install the system themselves with remote support.

Procedures

This version of the NEX system consisted of a voice-activated assistant, ambient sensors (motion and contact sensors), and a wearable accelerometer-based watch device. All aspects of the trial and interactions between the participants and the research team took place remotely over Zoom and via email and phone. The Friendly trial finished in September 2021, and the data analysis will be finalized by March 2022. The investigators will assess the technical performance of the NEX system by analyzing aspects of front-end usability (examining bugs and number of crashes, etc) and back-end issues (eg, memory and database integrity). Lighthouse analytics will be used for technology performance statistics. Participant engagement was also investigated by analyzing the data collected from the technologies to identify usual behavior patterns over time (periodicity). Data modeling based on a sliding window and association rule mining was completed with dietary intake data reported by participants, and sensor and smart plug data from their kitchens to identify eating occasions. Participants also completed a process evaluation interview and questionnaires (adapted version of the Technology Acceptance Model) [25] and System Usability Scale [26] to assess the acceptability and usability of technology devices. Process evaluation interviews (questions based on the Theoretical Domains Framework of behavior change [27]) were transcribed, and thematic analysis [23] was performed.

Phase 3: The Action Research Cycle

Study Overview

The final phase of the overall NEX project aims to demonstrate a refined NEX system working in a home environment. The first objective of this study is to use the NEX system to collect data for the automatic identification of patterns of typical behavior (periodicity) for the identification of ADLs. ADLs are essential and routine tasks that most healthy individuals can perform without assistance [28]. The inability to accomplish essential ADL may lead to unsafe conditions and poor quality of life and may indicate a physical or cognitive disability in older adults [29]. Eligibility for home care is frequently associated with deficits in ADL ability [30,31]. Assessment of ADLs through self-reported, observed, or objective data provides evidence to individuals and caregivers of deficits in self-care ability and supports potential interventions that may be required for continued independence [32]. The investigators aim to focus

on using sensors and smart plugs to facilitate the identification of the following ADLs: (1) eating and drinking events, (2) dressing, (3) bathing or showering, (4) getting up from and going to bed, (5) activity around the house, and (6) time spent outside the house.

A secondary research objective is to investigate the participants' engagement with the system by completing interviews with participants about their experience of using the NEX system and about system acceptability and usability. From a person-centered and ethical viewpoint, it is expected that NEX technology will have a positive impact on older users' lives. Therefore, it is valuable to investigate user psychological factors such as current mental well-being, satisfaction with current levels of daily novelty and participation in meaningful activity, and levels of general self-efficacy not only to facilitate building richer user profiles for technology developers but also to facilitate the exploration of the extent to which this technology may affect (positively or otherwise) these important life areas. Finally, the third research objective of this study is to recruit caregivers (n=5) and present caregiver participants with NEX system data to investigate the perceived usefulness of assisting with the provision of care to older adults.

Participants

For the purposes of this research trial, the investigators will aim to recruit a target sample size of n=30 (the sample size is based on population sizes from other published studies in this area) [33,34]. healthy older adults (aged ≥60 years) who live independently at home in the community. All participants must have the capacity to provide consent and be willing to provide informed consent to participate. For the purposes of this research, *healthy older adults* are defined as adults aged ≥60 years, living independently with or without one or more stable chronic conditions. In addition to testing a refined NEX system in this trial, the investigators aim to develop a new technology that will distinguish sensor interactions in households with frequent visitors. Participant recruitment commenced in November 2021, with an anticipated start date for the Action Research Cycle trial of January 2022.

Procedures

Eligible participants will enroll in the Action Research Cycle study for a minimum of 12 weeks, which will involve a mixture of in-home visits with a NEX project researcher and technician, and study visits will be conducted via Zoom. During the first visit, participants will complete an informed consent form, a demographics questionnaire, a questionnaire about technology use, and a compilation of health and well-being assessments. These assessments include health-related quality of life (EQ-5D-5L) [35], frailty assessment (Program of Research to Integrate Services for the Maintenance of Autonomy—PRISMA [Program of Research on the Integration of Services for the Maintenance of Autonomy] 7) [36], and Minicog (assessing memory and cognitive function) assessment [37]. In addition, the researchers (CMT, EH, and SK) will complete the following questionnaires: Novelty Need Satisfaction Scale [38], General Self-Efficacy Scale [39], Preference for Routine Scale [40], Meaningful Activity Participation Assessment [41] and Warwick-Edinburgh Mental Well-being Scale [42]. These measures, which have been previously used in other studies involving older adults [38,40-43], will facilitate an exploration of the extent to which the NEX system addresses these diverse needs. All assessments will be completed by a researcher in person or over a Zoom call where possible. At the end of this visit, the researcher will ask the participant for their Wi-Fi name and password so that all technologies can be preconfigured and paired to their network before installation in visit 2.

During the second visit, a researcher and technical engineer visited the participant in their home environment to facilitate the installation of the NEX system technology. The researcher and technician will complete a home configuration assessment with the participant by identifying the most appropriate locations to install NEX system technology. The technology that is integrated to form the NEX system is listed in Textbox 2, and an overview of the final system design is depicted in Figure 1.

Textbox 2. The technology components of the Action Research Cycle trial NEX system.

Action Research Cycle trial NEX system components

- Withings Smartwatch
- Amazon Echo show 8
- Aeotec hub
- Aeotec door and window sensor 7
- Aeotec multisensory 6
- Aeotec Smart Switch 6 (smart plugs)
- Lenovo smart tablet M8
- Danalto positioning wearable device with associated hubs
- Cloud-hosted secure device management, identity, and activities of daily living analytic engines

The above technologies will be deployed in combination to facilitate the detection of some of the key ADL from the participants' sensor, wearable, and smart plug use data over the trial period. The system will be installed in the homes of the participants by a technical engineer from DAVRA during this visit. Training on the technology will be provided to the participants at the time of installation, and a training manual will be provided. Specifically, participants will be shown how

to use their step count and sleep data via an app on the tablet provided, as well as how to use the entertainment functionality of Alexa Echo Show 8, for example, listen to the radio or ask questions, and how to set reminders, for example, to take medication. A dedicated NEX mobile helpline will be set up so that the participants can contact the research team with any problems at any time during the trial. The technical engineer will also be available via a technical helpline to consult or visit the participant if any of the technologies stop working. The participants are free to interact with the technology as little or as often as they wish during the trial period. Over the course of the trial, a NEX researcher will meet with the participants over Zoom on 4 separate occasions. During these interactions, participants (and their respective caregivers for n=5 participants) will be trained on how to interpret the data collected from the NEX system installed in their homes. Caregiver participants will be presented with a sample of raw data and ADL data collected from the technology installed in the homes of the older adults to whom they provide care. Caregivers will be interviewed about their perceptions of these data and the perceived usefulness of having access to these data when providing care and support. The research team will also investigate the perceived usefulness of these data for older adult participants trailing the NEX system in their homes. In addition, the researchers will gather ground truth data to validate the ADL data recorded via the technology; for example, What time did you get up from bed yesterday morning? During the final visit, the researcher will interview the participants about their experience of the trial, their experience and perception of each technology, and the NEX system as a whole, and complete an assessment of the system acceptability and usability (adapted version of the Technology Acceptance Model [25] and System Usability Scale [26]). In addition to the data collected as part of these questionnaires, the research team will consider the overall use and interaction with the NEX system technology; for example, smart plug use data and wearable devices, from the data collected over the trial period to understand the overall usability and acceptance of the system. The researcher will also repeat the EQ-5D-5L [33], Novelty Need Satisfaction Scale [38], General Self-Efficacy Scale [39], Preference for Routine Scale [40], Meaningful Activity Participation Assessment [41], and Warwick-Edinburgh Mental Well-being Scale [42] to investigate whether having NEX installed in participants' homes for the duration of the trial affects their quality of life and other aspects of life. The NEX system will subsequently be removed from the participants' homes by the NEX project technical engineer.

Ethics Approval

Participants in phases 1 and 2 were recruited via older adults, family caregivers, and health care professional organizations in Ireland. Participants were also recruited via DCU's Age Friendly University network, local council age friendly offices, and social media campaigns on Facebook and Twitter. Recruitment for phase 3 will follow a strategy similar to phase 2. Phases 1, 2, and 3 of the projects are not considered to have exposed participants to danger or discomfort. As phases 2 and 3 relate to the installation of technologies in the homes of older adults, there is a low risk that participants may become distressed or overwhelmed by this experience. To mitigate this, a support phone line was established, and regular communication between the participants and the research is a core feature of the project. In the unlikely event that participants become distressed, the research team will discuss the difficulty with the participant and help them reflect on the best course of immediate action. This may include taking a break from the trial, having the technology uninstalled from their homes, discontinuing participation, or, if necessary, with their consent, referring them to the project principal investigator. The investigators have explicitly highlighted to the DCU ethics committee and to participants that the NEX system data will not be monitored in real time; therefore, no intervention will be performed. If the researcher or participant has any concerns related to these questionnaires and assessments, the results will be sensitively discussed with participants, and they will be encouraged to speak to their general practitioner. Participation is voluntary, and oral and written information will be provided to participants regarding the purpose of the study and how their data will be used in the research. Ethical approval to conduct this study was obtained from the DCU Research Ethics Committee for phase 1 (DCUREC2019223), phase 2 (DCUREC2020180), and phase 3 (DCUREC202221).

Results

The project is funded for a 3-year period (2019-2022), and enrollment for phase 1 was completed in 2020. In phase 1, 426 participants (older adults, family caregivers, and health care professionals) were recruited to participate in research activities (face-to-face focus groups, web-based surveys, and web-based focus groups) to identify user needs and requirements to inform the development of the NEX system. Phase 2, which focused on pilot testing of the initial version of the NEX system, was completed in September 2021. A total of 6 older adult participants installed the NEX system technology in their home environments with remote support and completed a 10-week trial. Although the small sample size of participants makes it difficult to generalize the acceptability results, the technical evaluation and feedback from the Friendly trial will be used to refine the design of the NEX system for larger-scale deployment in the homes of 30 older adult participants (phase 3), which is expected to be completed by June 2022. Ethical approval for phase 3 was granted in November 2021, and the first results (phase 1) are expected to be submitted for publication in March 2022.

Discussion

Principal Findings

The NEX project brings together citizens, partners from the fields of health, technology, data analytics, and industry to develop timely technological solutions to support older adults living independently. The findings of phases 1 and 2 have informed the design of the NEX system, which has facilitated the collection of rich and extensive health and activity data from users' home environments. It is anticipated that the findings of phase 3 will indicate the potential usefulness of the ADL

detection and periodicity data approach for facilitating future IoT interventions in-home and community environments.

Although positive advances have been made in this area of research, there are significant challenges related to the usability and acceptability of IoT technologies for supporting independent living [5]. Specific issues related to the deployment of the technologies; that is, inaccurate sensors, battery or power issues, restricting users within the monitoring area, and lack of interoperability. In addition, the lack of user-centered design approaches in the development phases may also contribute to the low usability observed in some instances [5]. A particular strength of this study relates to the emphasis on user-centered design approaches involving multiple key stakeholder groups in phase 1. However, it remains to be seen whether the acceptability of the NEX system and the accuracy of the sensor data collected will be impacted by the technical issues described above.

An important consideration for the future development of NEX systems relates to how to deliver the data generated by the NEX system in an intuitive and easy-to-interpret manner. This is necessary to ensure that older adults can easily access their data to facilitate insight into their ADLs. Self-awareness of age-related changes and how they impact ADLs in a personal context is especially important for developing appropriate strategies to address these changes [44].

Conclusions

Although further research is warranted, it is anticipated that the findings of the NEX project will contribute to the design and development of future robust studies involving the trailing of IoT technologies in-home environments for older adults.

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Authors' Contributions

CMT wrote the manuscript. All authors reviewed the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ADL: activities of daily living
DCU: Dublin City University
IoT: Internet of Things
PRISMA: Program of Research on the Integration of Services for the Maintenance of Autonomy
UNR: user needs requirements

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Protocol

Lessening Organ Dysfunction With Vitamin C (LOVIT) Trial: Statistical Analysis Plan

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Abstract

Background: The LOVIT (Lessening Organ Dysfunction with Vitamin C) trial is a blinded multicenter randomized clinical trial comparing high-dose intravenous vitamin C to placebo in patients admitted to the intensive care unit with proven or suspected infection as the main diagnosis and receiving a vasopressor.

Objective: We aim to describe a prespecified statistical analysis plan (SAP) for the LOVIT trial prior to unblinding and locking of the trial database.

Methods: The SAP was designed by the LOVIT principal investigators and statisticians, and approved by the steering committee and coinvestigators. The SAP defines the primary and secondary outcomes, and describes the planned primary, secondary, and subgroup analyses.

Results: The SAP includes a draft participant flow diagram, tables, and planned figures. The primary outcome is a composite of mortality and persistent organ dysfunction (receipt of mechanical ventilation, vasopressors, or new renal replacement therapy) at 28 days, where day 1 is the day of randomization. All analyses will use a frequentist statistical framework. The analysis of the primary outcome will estimate the risk ratio and 95% CI in a generalized linear mixed model with binomial distribution and log link, with site as a random effect. We will perform a secondary analysis adjusting for prespecified baseline clinical variables. Subgroup analyses will include age, sex, frailty, severity of illness, Sepsis-3 definition of septic shock, baseline ascorbic acid level, and COVID-19 status.

Conclusions: We have developed an SAP for the LOVIT trial and will adhere to it in the analysis phase.

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KEYWORDS

sepsis; vitamin C; statistical analysis; organ; ascorbic acid; critical care; organ dysfunction; intensive care unit; intensive care; patient; vasopressor; infection; intravenous; health data; trial database; patient outcome; mortality; statistical framework; binomial distribution

Introduction

Sepsis, defined as a dysregulated host immune response to infection that leads to organ dysfunction and death [1], is a major global public health concern, causing up to 5.3 million deaths every year. Current sepsis management is focused on prompt antimicrobial therapy and organ-supportive care, and numerous trials of interventions for immune dysregulation have not demonstrated benefit [2]. Vitamin C is an endogenous antioxidant with multiple actions, including scavenging of oxygen radicals, restoration of endothelial function, and synthesis of norepinephrine and vasopressin as a cofactor. The findings of low vitamin C levels in critical illness and its association with poor outcomes have led to randomized clinical trials (RCTs) of intravenous vitamin C [3], including in sepsis [4], with variable results that do not exclude clinically meaningful improvements in patient outcomes.

The LOVIT (Lessening Organ Dysfunction with Vitamin C) trial is the largest trial to evaluate high-dose intravenous vitamin C in adults with sepsis. We aim to describe a prespecified statistical analysis plan (SAP) for the LOVIT trial. This SAP was written before data collection was complete for the last adult enrolled in the trial and prior to database lock and unblinding of the study team.

Methods

Design

The LOVIT trial is a multicenter, parallel-group, allocation-concealed, blinded (participants, clinicians, study personnel, members of the executive and steering committees, and data analysts) superiority RCT, which was registered on September 21, 2018 (ClinicalTrials.gov identifier: NCT03680274). The trial protocol has been published [5]; the final version (7.0) is dated February 15, 2021. The primary aim of the LOVIT trial is to determine whether intravenous vitamin C, administered to adults with sepsis receiving a vasopressor, reduces the composite outcome of mortality and persistent organ dysfunction [6] at day 28, when compared with placebo. Persistent organ dysfunction is defined as dependency on vasopressors, mechanical ventilation, or incident renal replacement therapy.

Sites

The trial involves 35 sites in Canada, New Zealand, and France.

Inclusion Criteria

Patients were eligible for inclusion if they were (1) at least 18 years old; (2) admitted to an intensive care unit (ICU) with proven or suspected infection as the main diagnosis; and (3) treated with a continuous intravenous vasopressor infusion (norepinephrine, epinephrine, vasopressin, dopamine, or phenylephrine [or metaraminol in New Zealand]) at the time of eligibility assessment and at randomization.

The LOVIT trial was designed before the COVID-19 pandemic, but patients with SARS-CoV-2 infection who otherwise met the eligibility criteria were eligible for the trial.

Exclusion Criteria

Patients were excluded for any of the following reasons: (1) more than 24 hours since ICU admission; (2) known glucose-6-phosphate dehydrogenase deficiency; (3) pregnancy; (4) known allergy to vitamin C; (5) known kidney stones within the past 1 year; (6) received any intravenous vitamin C during the current hospitalization, unless incorporated as part of parenteral nutrition; (7) expected death or withdrawal of life-sustaining treatments within 48 hours; (8) previously enrolled in this study (LOVIT trial); and (9) enrolled in a trial for which co-enrollment was not possible (determined on a case-by-case basis by discussion with the other trial's principal investigators).

Randomization

Trial participants were randomized in a 1:1 ratio to vitamin C or matching placebo using permuted blocks of variable size, undisclosed to study personnel, and stratified by clinical site using a web-based randomization interface. Pharmacists and technicians preparing the study medication (vitamin C or placebo) at each participating site were unblinded.

Intervention

The experimental intervention was intravenous vitamin C, administered in bolus doses of 50 mg/kg actual body weight, given every 6 hours for 96 hours (ie, 200 mg/kg/day and 16 doses in total), as long as the patient remained in the ICU. For patients weighing ≥150 kg, the weight was considered as 150 kg to calculate the dose. Each dose was administered over 30-60 minutes, except for participants >120 kg, for whom the infusion time was prolonged so that the rate did not exceed 100 mg/min. Participants in the control arm received 5% dextrose or normal saline in a volume to match the vitamin C. Placebo was infused over the same period as per the instructions for vitamin C, and was identical in color and other physical properties to vitamin C. Administration of open-label vitamin C in either group was not permitted and constituted a protocol violation.

Primary Outcome

The primary outcome is a composite of mortality and persistent organ dysfunction (defined as dependency on vasopressors, mechanical ventilation, or new renal replacement therapy) at day 28 [6]. Mechanical ventilation refers to invasive ventilation only, and patients receiving chronic renal replacement therapy before the index hospitalization do not meet the criteria for persistent organ dysfunction on the basis of ongoing renal replacement therapy. Note that day 1 refers to the day of randomization.

Secondary Outcomes

Efficacy outcomes include the following:

1. Persistent organ dysfunction–free days in the ICU, defined as the number of days alive and not dependent on vasopressors, mechanical ventilation, or new renal replacement therapy, up to day 28 and while in the ICU. Patients who die on or before day 28 will be assigned a value of −1 (modified from a previous report [7]). Any patient not receiving renal replacement therapy on a given day will be counted as renal replacement therapy–free for that day, even if renal replacement therapy is delivered on the day before or after this renal replacement therapy–free day. For patients on chronic renal replacement therapy before ICU admission, renal replacement after randomization will not be counted as organ dysfunction. Patients discharged from the ICU to a hospital ward before day 28 and who receive renal replacement therapy after ICU discharge will not be counted as having persistent organ dysfunction after ICU discharge. Patients discharged from the study ICU to another hospital's ward or ICU before day 28 and not receiving these interventions at discharge will be assumed to not be receiving them at day 28 if specific information is unavailable. Similarly, patients discharged from the study ICU to another hospital's ICU before day 28 and receiving any of these interventions at discharge from the study ICU will be assumed to be receiving them at day 28 if specific information is unavailable.
2. Mortality at 6 months.
3. Health-related quality of life (HRQoL) in 6-month survivors, as assessed using the 5-level EuroQol 5 dimensions [8] questionnaire. This scale evaluates mobility, personal care, usual activities, pain/discomfort, and anxiety/depression, and categorizes each of these dimensions into 5 levels that range from no problems to extreme problems. Respondents also evaluate their overall health status using a 100-point scale.
4. Global tissue dysoxia assessed at days 1, 3, and 7, measured by serum lactate levels [9]. This is assessed using liquid chromatography coupled with tandem mass spectrometry.
5. Organ function (including renal function) assessed by the sequential organ failure assessment (SOFA) score [10] at days 1, 2, 3, 4, 7, 10, 14, and 28. The SOFA score on day 1 may have included physiological data obtained after administration of study medication.
6. Inflammation at days 1, 3, and 7, assessed by serum interleukin-1 beta, tumor necrosis factor-alpha, and C-reactive protein levels, measured by Luminex (Luminex Corp).
7. Infection biomarker (serum procalcitonin [11]) levels at days 1, 3, and 7, measured using an enzyme-linked immunosorbent assay.
8. Endothelial injury at days 1, 3, and 7, assessed by serum thrombomodulin [11] and angiopoietin-2 levels [12], measured by Luminex.

Biomarker outcomes were measured only in patients enrolled in Canada. We included day 1 measurements of biomarkers in the outcome list above for completeness, although day 1 samples were taken before administration of the first dose of study medication, and these samples therefore provided baseline measurements. Biomarker analyses were conducted in a central study laboratory; due to delays in obtaining assays to measure procalcitonin and C-reactive protein, analyses of those secondary outcomes may be delayed and reported after the primary publication.

Safety outcomes include the following:

1. Stage 3 acute kidney injury as defined by Kidney Disease-Improving Global Outcomes criteria [13], using either serum creatinine or urine output criteria, at any time during the ICU stay.
2. Acute hemolysis, ascertained until 12 hours after the last dose of study medication, defined as clinician judgment of hemolysis, as recorded in the chart, or a hemoglobin drop of at least 25 g/L within 24 hours of a dose of study medication and 2 of the following: reticulocyte count >2 times the upper limit of normal; haptoglobin less than the lower limit of normal; indirect (unconjugated) bilirubin >2 times the upper limit of normal; or lactate dehydrogenase >2 times the upper limit of normal. Normal values are as defined at each participating center's laboratory. Severe hemolysis is defined as hemoglobin <75 g/L, at least 2 of the above criteria, and the requirement for transfusion of at least 2 units of packed red blood cells. As a secondary assessment of this acute hemolysis and of severe hemolysis, medical records of patients flagged as having hemolysis will be adjudicated by 2 blinded steering committee members, and any patient with hemolysis judged at least possibly related to the study drug after adjudication will be counted.
3. Hypoglycemia, defined as a blood glucose level measured in the hospital core laboratory of less than 3.8 mmol/L. Vitamin C therapy may be associated with falsely elevated glycemic readings when certain point-of-care glucometers are used to measure blood glucose [14]. Because elevated glycemic values may prompt iatrogenic hypoglycemic episodes if insulin or oral hypoglycemic agents are administered, hypoglycemic events will be reported as a safety outcome.

After trial registration and publication of the trial protocol [5], we added the secondary outcome of mortality at 28 days, which is a component of the primary outcome. The trial registration reports 3 other outcomes (vitamin C volume of distribution, clearance, and plasma concentration) that are only relevant for a pharmacokinetic substudy, whose analysis plan will be reported separately.

Adverse Events

Following Canadian recommendations for adverse event reporting in academic critical care trials [15], expected adverse events (death, stage 3 acute kidney injury, hemolysis, and hypoglycemia), whether severe or not, are prespecified trial outcomes and will not be reported separately as adverse events. Unexpected adverse events that are serious (ie, fatal, life-threatening, prolonging hospital stay, resulting in persistent or significant disability or incapacity, or constituting an important medical event according to the local principal

investigator) and considered by the local principal investigator to be at least possibly related to trial procedures will be reported to the coordinating center within 24 hours of becoming aware of the event.

Sample Size

We determined a minimum sample size of 800 participants based on the following assumptions. We established that an absolute difference of 10% in the composite outcome of mortality and persistent organ dysfunction (15% to 25% relative risk reduction) would be plausible [16,17] and sufficiently large to change practice. Based on recent clinical trials in a similar population [18], the risk of 28-day persistent organ dysfunction or mortality in the control arm was expected to be approximately 50%. By enrolling 385 evaluable patients per arm, the study would have 80% power to detect a 10% absolute risk reduction (from 50% to 40%, which corresponds to a 20% relative risk reduction). To account for consent withdrawal and loss to follow-up, we planned to enroll 400 patients per arm. Because of the subsequent COVID-19 pandemic, which started after the LOVIT trial had commenced recruiting and constituted extenuating circumstances [19], the steering committee approved the inclusion of eligible patients in whom SARS-CoV-2 infection was the cause of sepsis. However, in view of the unclear responsiveness of sepsis in the context of COVID-19 to vitamin C, the total sample size was increased to ensure that the original planned sample size (n=800) of non–COVID-19 participants was reached. We have planned a subgroup analysis based on COVID-19 status (mentioned below).

Statistical Analysis

Interim Analyses

The independent Data and Safety Monitoring Committee (DSMC) reviewed data on all serious unexpected adverse events at least possibly related to the study medication, in addition to hemolysis, stage 3 acute kidney injury, and hypoglycemia, after enrollment of 250 and 530 patients. The statistical plan for the interim analyses was included in the DSMC charter, which was written before enrollment of the first patient in the trial, and included in the protocol [5]. In an unadjusted analysis using a chi-square or Fisher exact test as appropriate, if the 1-sided *P* value had been <.1 (in the direction of harm in the vitamin C arm) for any of the 3 safety outcomes, an interim 2-sided analysis of the primary outcome would have been conducted. The DSMC could also have requested an analysis of the primary outcome at any time. This analysis would have generated a conditional power for showing statistically significant efficacy (superiority of vitamin C) in the final analysis of the primary outcome, assuming that the group-specific event rates observed to date had remained the same in the total sample size. If the conditional power for efficacy had been <20%, in the context of a 1-sided *P* value <.1 for any of the safety outcomes, the DSMC could have recommended stopping the trial to the steering committee. The DSMC could have made a similar recommendation even if these exact thresholds had not been met, based on its interpretation of the balance between safety and efficacy. At the second interim analysis, the DSMC performed an analysis of 28-day mortality and could have recommended stopping the trial to the steering committee at a 2-sided *P* value <.001. This Haybittle-Peto stopping boundary only trivially inflates the overall type I error, so a *P* value <.05 will be used to declare statistical significance in the final analysis [20].

After both interim analyses, the DSMC recommended continuation of enrollment as planned.

Intention-to-Treat Principle

We will analyze data from participants in the group to which they were allocated irrespective of protocol adherence. If ineligible participants were randomized, we will allow postrandomization exclusions only if they meet all of the following conditions: (1) the information about ineligibility was available at randomization; (2) participants did not receive the assigned intervention; (3) blinding was maintained; and (4) 2 members of the steering committee blinded to allocation agree that the participant was mistakenly randomized after review of information from medical records available at the time of randomization [21,22]. Patients who withdraw consent for their follow-up data to be used will also be excluded from the analyses.

Other Principles

The RCT will be analyzed using a frequentist approach. All statistical tests will be 2-sided, and the overall type 1 error for the primary outcome will be 5% at a significance level of .05. We will not report *P* values for secondary outcomes and analyses. All estimates of treatment effect will be reported with 95% CIs.

Categorical variables will be summarized with counts and percentages (based on the number of patients with data), and continuous variables will be reported as mean (SD) or median (IQR) as appropriate.

The main LOVIT manuscript will include analyses of the primary outcome and all secondary efficacy and safety outcomes, except for procalcitonin and C-reactive protein, as noted above. Unadjusted and adjusted analyses of the primary outcome and of 28-day mortality will be reported (see below); analyses of all other secondary outcomes will be unadjusted for baseline covariates.

Secondary outcome analyses will be performed regardless of the result for the primary outcome and will be considered exploratory.

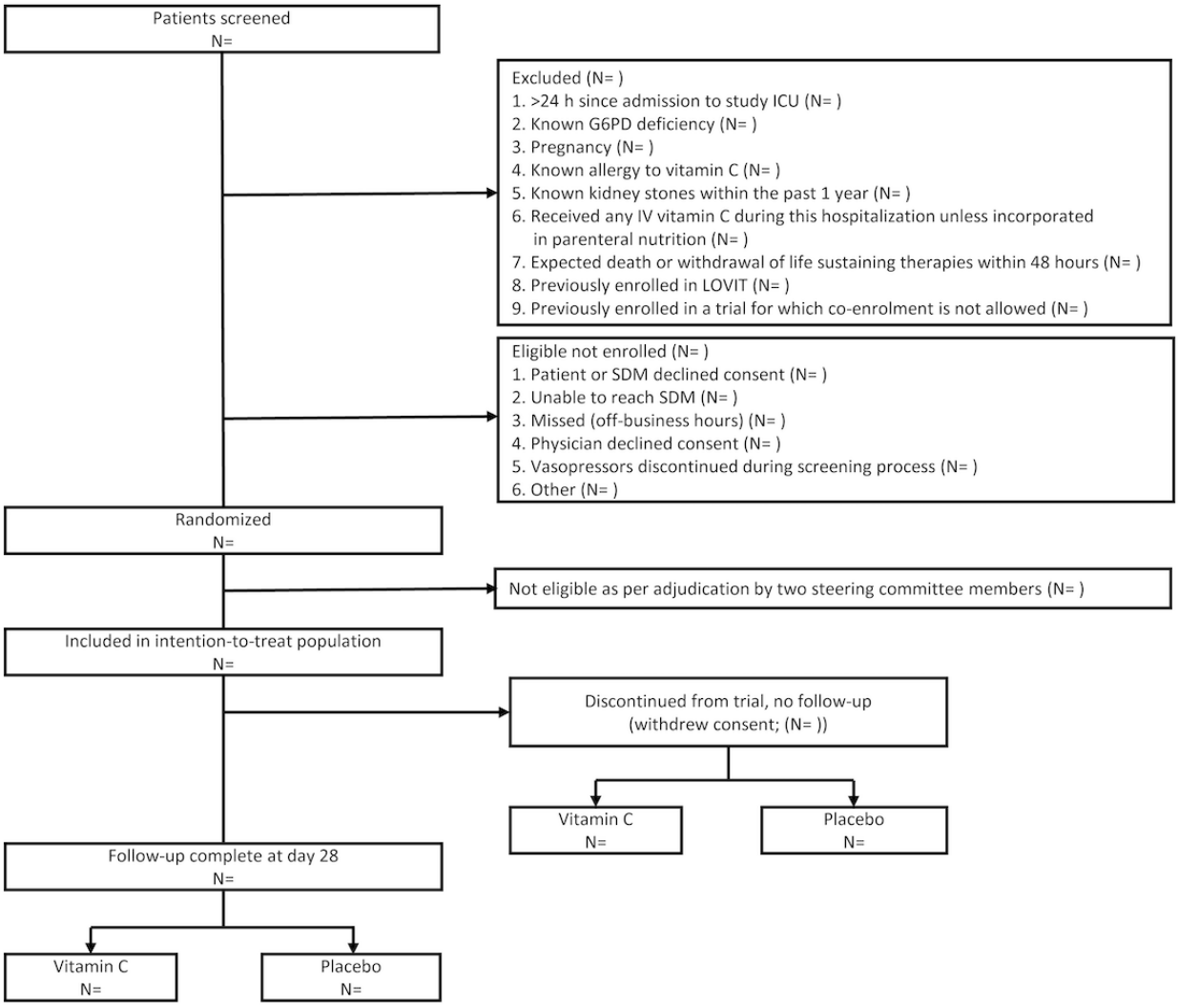
Subgroup analyses will be performed regardless of the result for the primary outcome.

Analyses will be conducted using SAS 9.4 (SAS Institute Inc) and R 4.0.3 (R Foundation for Statistical Computing).

Trial Profile

The flow of patients through the trial will be shown in a CONSORT (Consolidated Standards of Reporting Trials) figure (Figure 1) [23]. The figure will show the number of patients who fulfilled eligibility criteria, the number randomized, and the number analyzed for the primary outcome. Reasons for eligible patients not randomized and for exclusion after randomization will be given.

Figure 1. Flow of patients through the trial. G6PD: glucose-6-phosphate dehydrogenase; IV: intravenous; LOVIT: Lessening Organ Dysfunction with Vitamin C; SDM: substitute decision-maker.



Baseline Characteristics

A table (Figure 2) will be used to display baseline characteristics for the entire trial population and according to the allocated group. These characteristics will include demographics, comorbidities, location of suspected infection, severity of illness, organ support (mechanical ventilation and renal replacement therapy), and laboratory data.

Figure 2. Table 1 in the main manuscript (baseline characteristics).

Characteristic	All patients	Vitamin C (n=)	Placebo (n=)
Age, years; mean (SD)			
Sex, n (%) Male Female			
Admission type,[1] n (%) Medical Emergency surgery Elective surgery			
APACHE II score; mean (SD)			
SOFA score;[2] mean (SD)			
Clinical Frailty Scale; mean (SD)			
Primary site of infection, n (%) Pulmonary Gastrointestinal/ intra-abdominal Blood Skin or soft tissue Urinary Central nervous system Other			
SARS-CoV-2 positive,[3] n (%)			
Lactate (mmol/L); mean (SD)			
Ascorbic acid level (µmol/L); mean (SD)			
Sepsis-3 definition met[4]			
Time from ICU admission to randomization, hours; mean (SD)			
Comorbidities, n (%) End-stage renal disease (chronic dialysis) Diabetes mellitus (type 1 or 2)			
Treatments, n (%) Corticosteroids Mechanical ventilation Renal replacement therapy			

APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment

[1] Patients with emergency or elective surgical admission came to the intensive care unit from the operating room or post-anaesthetic care unit.

[2] This SOFA score is recorded on day 1 (randomization) but may include components measured after the first dose of study medication.

[3] In these patients, coronavirus disease 2019 was suspected at baseline and subsequently confirmed, or confirmed at baseline.

[4] The Sepsis-3 definition includes the requirement for a vasopressor infusion and lactate ≥2 mmol/L.

Adherence to the Protocol

Protocol adherence will be defined by the administration of at least 90% of scheduled doses of the study medication (vitamin C or placebo), until completion of the treatment protocol or ICU discharge, whichever comes first, and off-protocol administration of intravenous vitamin C.

Analysis of the Primary Outcome

For the principal analysis, we will report the number and percentage of patients who die or have persistent organ dysfunction at day 28. We will estimate the risk ratio and 95% CI in a generalized linear mixed model with binomial distribution and log link, with site as a random effect [24]. If this model does not converge, we will estimate the risk ratio using modified Poisson regression with small sample correction [25], and if that model also does not converge, we will estimate the odds ratio with logistic regression; both models will consider site as a random effect. We will use the same approach for the secondary analyses of the primary outcome and for analyses of binary secondary outcomes.

In secondary analyses of the primary outcome, we will adjust for prespecified baseline characteristics (age, sex, Acute Physiology and Chronic Health Evaluation [APACHE] II score [26], baseline receipt of corticosteroids, and time from ICU admission to randomization). Continuous adjustment variables will be modeled using restricted cubic splines with 4 knots to

account for nonlinear relationships with the log risk of the primary outcome. If more than 5% of the intention-to-treat population is excluded from this adjusted analysis because of missing baseline characteristics, we will impute missing data using multiple imputation with fully conditional specification to obtain 10 imputed data sets. The adjusted analysis will be performed on the imputed data sets, and the results will be pooled using Rubin rules so that both within- and between-imputation variances are counted. We will assume the APACHE II score is missing only if all its components are missing; otherwise, we will assume that a missing component has a normal value and calculate the APACHE II score accordingly.

For patients with missing data on the primary outcome or on the secondary outcome of 28-day mortality (eg, due to loss to follow-up), the principal and adjusted analyses will only include data on patients with outcome data. We will conduct a best case-worst case unadjusted sensitivity analysis, assuming first that all patients with missing data who received vitamin C did not have the outcome, whereas those in the placebo group did, and assuming second that the opposite states apply. If these analyses give discrepant results, namely statistically significant in one case but not the other or both statistically significant but in opposite directions, then we will use multiple imputation with fully conditional specification to explore the impact of missing data [27]. We acknowledge the limitations of this approach, given that outcome data may not be missing completely at random, and the importance of making all efforts to minimize the extent of missing outcome data.

Subgroup Analyses

We will evaluate the effect of vitamin C on the primary outcome in subgroups defined at baseline by age (<65 vs ≥65 years), sex (male vs female), frailty (Clinical Frailty Scale 1-4 vs ≥5 [28]), severity of illness (quartiles of predicted risk of death from the baseline APACHE II score), Sepsis-3 [1] definition of septic shock (vasopressor infusion required to maintain a mean arterial pressure of 65 mmHg and lactate ≥2 mmol/L vs vasopressor need alone), and baseline ascorbic acid level (as quartiles). We hypothesize that vitamin C is more beneficial in elderly patients, those with greater frailty and illness severity at baseline, those who meet strict criteria for septic shock, and those with lower baseline ascorbic acid levels. In addition to the 6 subgroups prespecified in our published protocol, we will assess for a subgroup effect based on COVID-19 status (positive result on polymerase chain reaction or a rapid antigen test at baseline vs negative), hypothesizing no evidence of a difference in treatment effect. We will report interaction terms from the generalized linear mixed model (as used in the principal analysis) with treatment group, subgroup, and their interaction, and display the results in a Forest plot. We will assess the credibility of any subgroup effect with interaction at $P<.05$, using a published tool [29].

Analyses of Secondary Outcomes

Unless noted, analyses will not be adjusted for baseline characteristics or for site.

Analyses of clinical secondary outcomes will proceed as presented below.

Mortality at Day 28

We will conduct a principal unadjusted analysis and secondary analysis adjusted for baseline characteristics and site according to the analysis plan for the primary outcome outlined above. We will also conduct a best case-worst case unadjusted sensitivity analysis to account for missing data, with multiple imputation for missing outcome data if these 2 sensitivity analyses differ (as for the primary outcome).

Six-Month Mortality

We will conduct a principal analysis using a Cox proportional hazards model, with site as a random effect. We have chosen a Cox model because we record the data of death for decedents and because differences in duration of survival are plausibly important over a 6-month time horizon. Patients who are lost to follow-up or who withdraw consent for follow-up will be censored at the last follow-up time (expected to be at hospital discharge).

Six-Month HRQoL

In survivors with complete follow-up, we will report the mean or median for each dimension of the scale and for the self-reported overall health status in each group. Differences in means or medians will be reported, as appropriate.

Persistent Organ Dysfunction–Free Days in the ICU (up to Day 28)

Analysis will be rank-based, with death assigned as −1 (modified from a previous report [7]). We will display an empirical cumulative distribution function for each group and report the median, along with a difference in medians.

SOFA Scores at Prespecified Time Points

Results by randomized group at each time point will be summarized descriptively and displayed in a boxplot. For scores during the first 7 days, we will use a linear mixed model to account for repeated measures, with a random intercept and time for each subject and a random effect for site. Because day 1 SOFA may not be a true baseline value, it will not be used to model SOFA on subsequent days. For patients who die before day 7, we will impute the worst (highest) value, and for patients discharged alive before day 7, we will impute the value based on data available for these patients. We will conduct a likelihood ratio test between the empty model and the one with time, group, and their interaction, and will conduct additional testing of the terms in the model only if that test is statistically significant. For SOFA scores beyond day 7, we will report differences in means or medians because of the expected large proportion of patients with missing data due to death or discharge from the ICU.

For each biomarker outcome, results by randomized group at each time point will be summarized descriptively and displayed in boxplots. We will use constrained longitudinal data analysis [30] to analyze biomarker results. At day 3 and day 7, groups will be compared using a linear mixed model and adjusting for day 1 biomarker levels, with a random intercept for site and

unstructured within-patient covariance. Biomarker data will be transformed, if necessary, to satisfy model assumptions.

For safety outcomes, we will report the number and percentage of each prespecified safety outcome, and the number of unexpected serious adverse events and number of patients with an unexpected serious adverse event, in each treatment group. Differences will be reported as risk ratios.

Tables and Figures

Draft tables (Figures 2 and 3) and figures (Figure 1; Textbox 1) for the main manuscript are presented, and planned additional tables and figures are described in Multimedia Appendix 1.

Figure 3. Table 2 in the main manuscript (primary and secondary outcomes).

Primary Outcome	Vitamin C	Placebo	Measure of association (95% CI)
28-day mortality or POD, n (%)			
28-day mortality, n (%)			
POD at day 28, n (%)			
Secondary Outcomes			
POD-free days in ICU, up to day 28, n (%)			
6-month mortality, n (%)			
HRQoL (EQ-5D-5L score) at 6 months, mean (SD) EQ-VAS, mean (SD) Mobility Self-care Usual activities Pain/discomfort Anxiety/depression			
SOFA score; mean (SD) Day 2 Day 3 Day 4 Day 7 Day 10 Day 14 Day 28			
Safety endpoints			
Stage 3 acute kidney injury, n (%)			
Acute hemolysis, n (%) Adjudicated, n (%) Severe hemolysis, n (%) Adjudicated, n (%)			
Hypoglycemia, n (%)			
Serious adverse events, n (%)			

A p-value will only be reported for the primary outcome of 28-day mortality or POD.

HRQoL, health-related quality of life; POD, persistent organ dysfunction; SOFA, sequential organ failure assessment; VAS, visual assessment scale

Textbox 1. Additional figures planned for the main manuscript.

- Sequential organ failure assessment scores over days 1-7 in the vitamin C and placebo groups (displayed as a boxplot)
- Subgroup analyses (displayed as a Forest plot)

Funding, Registration, and Ethics Approval

The LOVIT trial is funded by a grant from the Lotte and John Hecht Memorial Foundation (grant 4318). The funder had no role in the design of the study, ongoing data collection, SAP or data interpretation, or writing of any associated manuscript.

The LOVIT trial was conducted with the support of the Canadian Critical Care Trials Group. The protocol has been approved by the Comité d'éthique de la recherche du Centre intégré universitaire de santé et de services sociaux de l'Estrie – Centre hospitalier universitaire de Sherbrooke (reference MP-31-2019-2945) and at each participating site. The LOVIT trial has been registered on ClinicalTrials.gov (NCT03680274; September 21, 2018).

Document History

Version 1 of the statistical analysis protocol, dated January 19, 2022, was posted to this trial's listing on ClinicalTrials.gov on January 20, 2022. This version contains corrections and clarifications, but no changes to the proposed analysis methods.

Results

As of July 19, 2021, enrollment in the trial has been completed. Follow-up data at 6 months were available by January 24, 2022, with results to follow based on this SAP.

Discussion

The LOVIT trial is a methodologically rigorous RCT of intravenous vitamin C monotherapy in critically ill patients with sepsis. This SAP, drafted before data collection was complete for the last patient enrolled in the trial and prior to database lock and unblinding of the study team, will guide the analysis of data from this trial.

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Patrick Archambault; Centre Intégré Universitaire de Santé et de Services Sociaux de Chaudière-Appalaches, Lévis, QC, Canada

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Troy Browne; Tauranga Hospital, Tauranga, New Zealand

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Geoffrey Shaw; Christchurch Hospital, Christchurch, New Zealand

Andrew Van Der Poll; Department of Critical Care Medicine, Auckland City Hospital, Auckland, New Zealand

Gordon Wood; Vancouver Island Health Authority, Victoria, BC, Canada

Conflicts of Interest

The LOVIT trial was funded by a grant from the Lotte and John Hecht Memorial Foundation to FLamontagne and NA, with funds held at Université de Sherbrooke and distributed to sites enrolling patients. DA declares grant funds from the French Ministry of Health to conduct a trial of vitamin C in adults with sepsis and acute respiratory distress syndrome. MC declares holding a patent licensed to SQI Diagnostic. The remaining authors have no conflicts of interest to declare.

Multimedia Appendix 1
Planned supplementary tables and figures.
[PDF File (Adobe PDF File), 228 KB - resprot_v11i5e36261_app1.pdf]

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Abbreviations

APACHE: Acute Physiology and Chronic Health Evaluation
DSMC: Data and Safety Monitoring Committee
HRQoL: health-related quality of life
ICU: intensive care unit
LOVIT: Lessening Organ Dysfunction with Vitamin C
RCT: randomized clinical trial
SAP: statistical analysis plan
SOFA: sequential organ failure assessment

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Corrigenda and Addenda

Metadata Correction: The Effects of a Virtual Reality–Based Training Program for Adolescents With Disruptive Behavior Problems on Cognitive Distortions and Treatment Motivation: Protocol for a Multiple Baseline Single-Case Experimental Design

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Related Article:

Correction of: https://www.researchprotocols.org/2022/5/e33555

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In "The Effects of a Virtual Reality–Based Training Program for Adolescents With Disruptive Behavior Problems on Cognitive Distortions and Treatment Motivation: Protocol for a Multiple Baseline Single-Case Experimental Design" (JMIR Res Protoc 2022;11(5):e33555) the authors noted an error.

In the originally published article, one of the affiliations of author Ramón J L Lindauer (*Child and Adolescent Psychiatry, Amsterdam UMC Location University of Amsterdam*) was inadvertently omitted. The corrected list of authors and their affiliations now appear as follows:

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The correction will appear in the online version of the paper on the JMIR Publications website on May 27, 2022, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Protocol

Insights About Cannabis and Psychosis Using Video Games for Young People With a First Episode of Psychosis, Particularly Those From Black Racialized Communities: Protocol for a Mixed Methods Study

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Abstract

Background: Cannabis use disorder among young people with a first episode of psychosis contributes to relapse, hospitalization, and impaired functioning. However, few studies have examined what young people with early phase psychosis, particularly those from Black racialized communities, understand or appreciate about this relationship, even though they may be at risk. There are no formally tested knowledge translation strategies that disseminate these research findings for young people with emerging psychosis from Black racialized communities.

Objective: This study aims to conceptualize what young people with early phase psychosis/cannabis use disorder understand about the relationship between cannabis and psychosis, focusing on people from racialized backgrounds. This study also aims to assess whether the knowledge translation product, the "Back to Reality Series," increases awareness of the impact of cannabis use on psychosis from the perspectives of young people with emerging psychosis and cannabis use disorder from Black African and Caribbean communities.

Methods: Qualitative analysis will reveal themes from qualitative interviews about cannabis and psychosis from the perspectives of young people with emerging psychosis and cannabis use disorder from Black African and Caribbean communities. Perceptions before and after exposure to the Back to Reality Series will be qualitatively analyzed. A control game will be used for comparison, and scores on a quiz after playing the Back to Reality Series will be quantitatively analyzed to establish whether the Back to Reality Series raises awareness of the effects of cannabis on psychosis. An advisory council involving young people from Black communities, family members, and clinicians will bring community perspectives to this research.

Results: We began recruiting participants for this study in September 2021. We will complete data collection on demographic and clinical factors, qualitative interviews, and quantitative assessments of the Back to Reality Series.

Conclusions: The voices of young people from racialized backgrounds will generate preliminary data to inform early psychosis programs, addressing cannabis use in this population. The findings may advance the use of a new knowledge translation product that deals with gaps in knowledge about cannabis use for people experiencing early phase psychosis, particularly those from racialized communities.

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KEYWORDS

first-episode psychosis; cannabis use; knowledge translation; Black youth; video games

Introduction

Background

Regular cannabis use (3 times a week or more) is widely recognized as a significant risk factor for relapse of psychosis among young people under 25 years experiencing emerging psychosis [1,2]. Hospitalizations for cannabis-related psychotic disorders in Canada have increased significantly from 2006 to 2015 [3]. Although the association is complex and multi-directional, variables that moderate this relationship include the age of first use [4], the frequency of use [4], the genetic vulnerability for schizophrenia [5-7], the delta-9-tetrahydrocannabinol (THC) content of cannabis [8], and previous psychosis symptoms [4,8]. The higher the THC content, the greater the risk [4,8]. Unfortunately, the people who would benefit the most from this information are often the least likely to know about it [9,10].

Studies suggest that patients experiencing a first episode of psychosis, who used cannabis but stopped, had fewer hospitalizations and had better functioning than those who never used or those who did not stop using [11]. Compared with those who stopped, patients with a first episode of psychosis and ongoing marijuana use were significantly more likely to relapse and experience readmissions [1].

There are no established therapies for cannabis use disorder in patients with a first episode of psychosis [12]. Pharmacotherapies have not yet been shown to be effective in this population [13]. Cognitive behavioral therapy (CBT) and motivational interviewing are not more effective than early psychosis intervention services alone for patients with a first episode of psychosis and cannabis use disorder [13,14]. Early psychosis intervention services provide care to youth and young people experiencing a first episode of psychosis [15], which can significantly reduce substance use [16], but many patients with a first episode of psychosis do not improve their substance use disorders or engage in substance use treatments [16]. Novel strategies are needed to augment the therapy offered by early psychosis intervention programs.

Insight About Cannabis and Psychosis

To gain insight, young people must first appreciate what psychosis is and the impact cannabis could have on their recovery. Increasing insight about the impact of cannabis use upon relapse might improve outcomes among young people with a first episode of psychosis and cannabis use disorder, primarily if this insight has occurred early in treatment. However, few studies have examined what young people with early phase psychosis understand about this relationship, even though they may be the ones most at risk. Few studies explore the viewpoints of people experiencing a first episode of psychosis on the link between substances of abuse and psychosis, let alone cannabis use. Most qualitative studies focus on people experiencing chronic illness [17]. However, there may be differences in how people with chronic schizophrenia conceptualize the impact of cannabis use on their health compared to those with emerging psychosis [18].

One of the few qualitative studies capturing participants' perspectives with a first episode of psychosis found a wide variety of beliefs [18]. Some patients drew connections between substances of abuse and the onset of psychosis. In contrast, others were unaware or did not believe there was an association [18]. Young people experiencing a first episode of psychosis reported several benefits of cannabis or other substances. Cannabis and other substances were viewed as social lubricants, enhancing the social milieu they experienced with their friends [19]. They felt it was a pleasurable activity that reduced anxiety, increased creativity, and increased enjoyment of music [19]. However, these young people also expressed concerns about their substance use [19]. This Canadian qualitative study suggested that some participants thought that cannabis use was more likely to trigger psychosis experiences compared with other substances [19]. Moreover, this study indicated that participants believed substances of abuse helped normalize their altered perceptions because their peer group shared time-limited yet similar psychosis-like experiences [19]. However, none of these studies focused specifically on cannabis.

Researchers and service providers need to understand what young people with emerging psychosis believe about cannabis. Understanding their perspectives may support the creation of targeted and effective strategies with the potential to improve their insight and ultimately engage them in cannabis reduction strategies. This need may be particularly poignant for young people with cannabis use disorder and a first episode of psychosis from racialized backgrounds.

Racialized Groups, Psychosis, and Cannabis

Compared with the native-born population, higher rates of psychosis incidence in Ontario have been reported among Black racialized immigrants to Canada [20]. For Black communities, cannabis use is built on a history of stigma, negative stereotypes, and criminalization [21]. Compared with young people from other ethnic groups, Black youth may be more susceptible to the adverse mental effects of cannabis use because of health and legal inequities. Significantly more patients with a first episode of psychosis and a substance use disorder, including cannabis, were arrested compared with their nonsubstance abusing counterparts, regardless of ethnicity [16]. However, an arrest may have more lasting consequences for young people from Black communities. More specifically, the self-reported rates of cannabis use in Toronto (2018) were higher for nonracialized youth under 19 years (39% nonracialized versus 14% Black). However, about 15% of underage Black youth were detained for bail hearings for cannabis possession. In comparison, only 3% from the comparable nonracialized group [22] experienced this consequence, suggesting underage Black youth experience more punitive legal ramifications when arrested for cannabis. A Canadian study involving adult respondents revealed a significantly higher odds ratio of problematic cannabis use among respondents who self-identified as Black Caribbean compared with the general Canadian population and people of Black African ethnicity [23]. The researchers defined “problematic use” as a pattern of use with a high probability of harm based on the World Health Organization Alcohol, Smoking, and Substance Involvement Screening Tool [23]. Heavy cannabis use appears to be more correlated with youth experiencing psychosis compared with other conditions. Black youth with a first episode of psychosis had a significantly higher frequency of cannabis use and smoked significantly more “joints” than Black youth with other mental health conditions [24]. In summary, these studies highlight the need for early intervention to support Black youth with emerging psychosis. Culturally grounded substance abuse programs exist for Black racialized communities, but these programs do not address psychosis [25]. A “one-size-fits-all” approach may not work for racialized groups who may need more targeted initiatives [26].

Video Games

Serious game design principles incorporate the following conceptual framework: learning by players, storytelling within the game, interactive gameplay, and user experiences to promote emotional engagement and prosocial attitudes [27]. At present, video games are an underused medium in health care, despite growing evidence supporting their educational effectiveness. A meta-analysis of randomized controlled trials on the effectiveness of serious video games revealed a significant increase in knowledge transfer among youth with chronic conditions compared with control games [28]. Serious video games can be a form of simulation-based training, testing new ideas and skills through interactive play [27,29,30]. Playing video games was ranked as one of the top 10 favorite activities among youth attending an early psychosis intervention program. Over 80% had access to smartphones and computers [31]. Video game technology helps depict psychosis-like experiences. A commercial video game, *Debris*, which was created with input from an industry-academia partnership, weaved psychosis simulations into the gameplay experience [32] as a means to mobilize concepts about psychosis to a general audience. Moonray Studios of Hamilton sold it to PlayStation 4 in 2019. *On Track<The Game* was designed to promote engagement in care among young people who have experienced a first episode of psychosis [33]. Qualitative and quantitative analyses revealed a significant increase in hope, engagement, empowerment, and recovery attitudes at baseline and 2 weeks after playing the game. Participants had an opportunity to use the interactivity to learn about psychosis and practice coping skills [33]. Virtual reality technology significantly reduced auditory hallucinations and paranoia among participants with a first episode of psychosis, when combined with CBT [34]. *Sparx* is a video game that uses avatars to train players to use CBT skills and has been shown to treat depression among adolescents [35]. Finally, successful strategies have combined multimedia campaigns and technology with community programs at schools or family doctors’ offices [36].

Rationale

The Back to Reality Series is an innovation using a medium that appeals to a traditionally more challenging cohort to engage in treatment. By simulating the experience of psychosis, the Back to Reality Series is expected to improve appreciation of the impact of cannabis use on psychosis. To date, the Back to Reality Series is the only set of video games in Canada or internationally that addresses cannabis use, pathways to care, and the risk of psychosis, inspired by data derived from studies involving people of Black African and Caribbean descent with a first episode of psychosis [37-39]. This project aims to evaluate the feasibility of the Back to Reality Series as a knowledge translation product for young people experiencing a first episode of psychosis, particularly those from Black communities. This knowledge translation approach aims to effectively disseminate the research knowledge to those who might benefit from understanding the risks.

This study will reveal how racial identity, gender, psychosis, and cannabis use intersect and uniquely impact the lives of young people with a first episode of psychosis and cannabis use disorder from Black racialized communities. It will involve a series of qualitative interviews and conversations with participants about cannabis and psychosis, digging deeper into their experiences to understand how these episodes shaped them. We explore what sets young people of Black African and Caribbean descent apart from other ethnicities regarding their cannabis use.

Study Aims

Perspectives on Cannabis and Psychosis

This study will examine the perceptions of the mental health effects of cannabis on psychosis based on young people's perspectives among Black African and Caribbean first- or second-generation immigrants with a first episode of psychosis and a cannabis use disorder. These perceptions will be explored before and after the use of the Back to Reality Series. To this end, the study will examine narratives, opinions, and personal experiences to elucidate how the relationship between cannabis and psychosis is processed to appreciate why they think the way they do. The study will outline the participants' understanding of the emotional, social, and mental health impacts of ongoing cannabis use on the first episode of psychosis. We will explore stories about the perceptions of the benefits and harms of cannabis, applying a race and gender lens to glean perspectives before and after playing the Back to Reality Series.

Insight and Knowledge Acquisition

The second objective is to establish the feasibility of using the Back to Reality Series to translate knowledge about the mental health effects of cannabis. Knowledge acquisition will be measured by comparing scores on a quiz after playing the Back to Reality Series versus a control game. After playing whichever game remains, the participants' perceptions of the effects of cannabis use on psychosis will be explored to converge qualitative data before and after playing the Back to Reality Series.

Development of a Strong Participatory and Community Engagement Component

The third objective is to develop a strong participatory and community engagement component based on the inclusion of an advisory council. The proposal builds on co-creation and capacity building, which increases the project's community relevance.

Methods

Design

This mixed methods study aims to conceptualize what young people with early phase psychosis/cannabis use disorder understand about the relationship between cannabis and psychosis, focusing on people from racialized backgrounds. All aspects of the research will be conducted virtually. Participants will be interviewed over Zoom, and the interviews will be video and audio recorded to observe emotional responses and to produce verbatim transcripts for qualitative analysis. Consent will be obtained over the Zoom platform. The research staff consisting of research students, research assistants, and a research coordinator will be invited to self-identify as one of the designated underrepresented groups in their cover letter (Black or person with lived experiences of psychosis and cannabis use). This process will help to increase concordance between researchers and participants, and foster safe spaces for dialogue around complex issues such as race and cannabis use [40]. The principal investigator will train the research staff. An advisory council will help create a knowledge dissemination plan involving the Back to Reality Series to generate ideas about promoting it to early psychosis intervention services and Black racialized communities. A French-language version of the Back to Reality Series is currently being developed, and 10 French-language participants will be recruited for this small-scale demonstration project once completed. The details of this protocol will be published elsewhere once the games have been translated into French.

Ethics Approval

Ethics approval has been obtained from the Hamilton Integrated Research Ethics Board (number 13417) and the Western Research Health Sciences Research Ethics Board in London, Ontario. Full approval was granted May 27, 2021 until April 20, 2022. On April 9, 2022 received an annual approval extension from April 20, 2022 to April 20, 2023. We are awaiting approval from the Toronto Academic Health Sciences Network, the Ottawa Health Science Network Research Ethics Board, and the Research Ethics Board of the CIUSSS de l'Ouest-de-l'île-de-Montréal.

Community Engagement

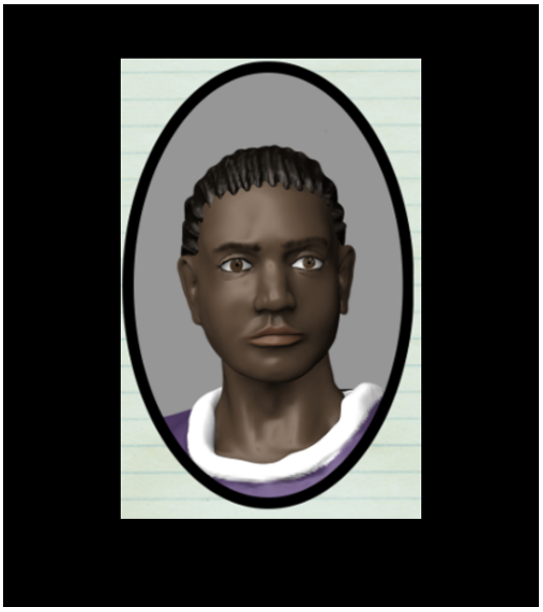
The advisory council will involve Black community members, clinicians, family members, Black youth, and young people with lived experiences. It will include engagement of the following community partners: young people from the Free for All Foundation, a charitable organization serving families and youth from Black communities in Brampton, Ontario; the Institute for the Advancement of Mental Health (formerly the Schizophrenia Society of Ontario), serving people with serious mental illness and their family members; and the Early Psychosis Intervention in Ontario Network, which involves over 50 early psychosis intervention clinical programs throughout the province of Ontario. The members will not be participants in the study. It is not a steering committee because the advisory council does not manage the operations of the research, manage the research progress, or conduct the research. The advisory council members advise the researchers about the research priorities and interpretations about the participants' perspectives on cannabis and psychosis, as well as their insights and knowledge acquisition after playing the game. The advisory council will engage in quarterly knowledge exchange meetings to (1) help develop a plan to disseminate the Back to Reality Series for young people, particularly youth from Black racialized communities, (2) reflect upon and review educational content inspired by the video games, (3) monitor and review the representation of psychosis and Black or racialized persons within the research findings, (4) give feedback about qualitative analysis of the findings, and (5) help integrate the Back to Reality Series into early intervention care or use by community agencies.

To create an environment where community members and people with lived experiences feel supported in participating in the research process, the advisory council will adopt the guidelines promoted by the Strategy for Patient-Oriented Research of the Canadian Institute for Health Research [41] as follows: mutual respect, clarification of roles, co-creation of knowledge, support and build on equity, diversity, and inclusion principles.

The Back to Reality Series and the Control Game Morpheus' Spell

The Back to Reality Series is a set of video games designed to increase knowledge about cannabis risks for underage youth and young people experiencing a first episode of psychosis. The Back to Reality Series consists of the following 3 video games: Harry's Journey, Harry's Journal, and Harry's PathwaysToCare Map (Figure 1). Harry's Journey tells the story of Harry (a teenager in his senior year of high school; second-generation Jamaican descent) who starts to experience psychosis after using cannabis regularly for 4 years. Harry's Journal takes scenes from Harry's Journey to illustrate psychiatric symptoms associated with psychosis. The PathwaysToCare Map displays 3D replicas of youth mental health and addiction services to help players navigate the mental health care system. It is novel because it uses gaming technology to portray psychosis and because the interactivity allows the players to explore the potential harms and benefits of cannabis use.

Figure 1. The Back to Reality Series character Harry.



Archie produced the games adopting serious game design methodology [27] with an integrated knowledge translation community involving Black youth, young people with lived experiences of cannabis and psychosis, family members, game designers, clinicians, and researchers [42]. Focus group feedback from family physicians revealed that the Back to Reality Series delivered content relevant for youth in their practice about mental health and addiction [43]. Family physicians recommended offering the games to youth while patients were waiting for their appointments.

There have been small demonstration projects to pilot the use of the Back to Reality Series. Ten participants between 17 to 30 years of age with a first episode of psychosis felt that Harry's Journey realistically portrayed psychosis experiences, and they enjoyed playing it [44]. Fifty-five youth experiencing homelessness (16-19 years of age) were randomized to play the Back to Reality Series versus a control game. Participants playing the Back to Reality Series demonstrated a significant mean knowledge test score advantage (mean 6.8, SD 1.6) compared to those playing the control game (mean 5.5, SD 1.9; P=.02) [45]. In 2020, 10 undergraduate students created tutorial objectives and content inspired by the Back to Reality Series. Using the Back to Reality Series as the focus of dialogue, student-led tutorials were conducted involving 9 Black youth (16-19 years of age) as participants. The participants demonstrated significant increases in their knowledge about cannabis, mental health, and pathways to care after playing the Back to Reality Series and engaging in the tutorials [42]. Qualitative analysis of the feedback revealed that the content was meaningful to them (eg "I guess the fact that Harry lived in a realistic teenage lifestyle that like a lot of youth can relate to and that made it more meaningful cause it felt more relevant.") [42].

The control game "Morpheus' Spell" is inert. It is a spelling "pop culture" digital game with no mental health content. It failed to increase knowledge about mental health and addiction when undergraduate students were randomized to play the Back to Reality Series first, obtaining a Psychosis and Cannabis Test (PCT) Quiz score of 7.55 (SD 1.04) versus a score of 7.82 (SD 0.40; P=.28) after playing the Back to Reality Series followed by Morpheus' Spell [46].

Visit 1: Baseline Assessments

Study Population

The eligibility criteria are as follows: (1) meet the criteria for a first episode of psychosis defined as the first illness episode involving psychosis symptoms; (2) meet DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition) criteria for a psychotic disorder and a lifetime or current cannabis use disorder (up to 45% of people with a first episode of psychosis will meet the criteria for cannabis use disorder [16,47,48]; patients diagnosed with cannabis-induced psychosis by definition meet the criteria for both conditions [49] and will be eligible); (3) be between the ages of 16 and 30 years; (4) self-identify as a Black African or Black Caribbean first- or second-generation immigrant (English speaking), or belong to

any ethnic group; (5) be a client of an early psychosis intervention with up to 12 months of service; and (6) be fluent in English.

Participants will self-identify and be divided into the following disaggregated ethnic and racialized groups: Black African (n=24), Black Caribbean (n=24), and any ethnicity (n=24). There may be significant differences in social and community norms for cannabis use between Black African and Caribbean groups and differences in English proficiency, educational attainment, and immigrant status. Sex will be defined based on sex assignment at birth. Gender will be self-assigned as man, woman, transgender, fluid, two-spirit, and non-binary. Equal numbers of men (including transmen) and women (including transwomen) will be enrolled for each racialized group. Participants will self-identify as nonimmigrant, or first- or second-generation immigrant.

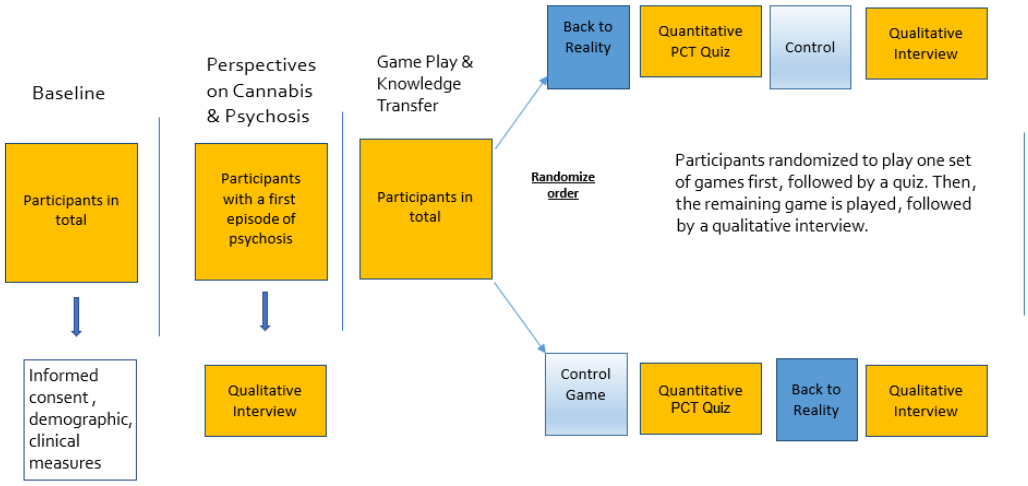
Recruitment of Study Participants

A convenience sample will be recruited. The following 5 early psychosis intervention sites will recruit the participants: London, Toronto, Hamilton, Ottawa, and Montreal. All early psychosis intervention sites share the same entrance criteria for admission and offer similar services. The sites provide a pool of over 1000 patients with a first episode of psychosis. Based on prior early intervention studies involving this population, at least 30% will be of Black African and Caribbean descent [37,39]. Staff at each site will receive training about recruitment, approach eligible clients, and obtain consent for the research coordinator to contact them. Participants can access laptops on loan from the study or, when pandemic restrictions allow, can access computers at early intervention programs.

Data Collection

This phase of the project involves baseline clinical assessments. Research staff will conduct an individual interview to obtain baseline demographic/clinical measures and illicit narratives exploring the perceptions of the effects of cannabis use on psychosis (Figure 2).

Figure 2. Study design. PCT: Psychosis and Cannabis Test.



Assessment

Demographic data will be collected on gender, sex, age, ethnicity, education, living circumstances, language, income, immigrant status (first or second generation), employment, disability status, and DSM-5 diagnoses.

Measures

Clinical and Sociodemographic Measures

The Diagnostic Assessment Research Tool (DART) for DSM-5 diagnoses [50] will be used as an interview guide to help establish the diagnosis. Baseline measures will also be drawn from demographic tools used in the Ontario Community Mental Health Evaluation Initiative [51]. This tool collects information on marital status, ethnicity, employment status, immigration status, and other sociodemographic characteristics.

Drug Use and Abuse

The prevalence rates of cannabis and alcohol use disorders will be assessed using the DART for lifetime and the 12-month period prior to the baseline assessments. The DART is an open-access semistructured interview developed by researchers at McMaster's Department of Psychiatry and Behavioral Neurosciences for clinical and research assessments of DSM-5 diagnoses for mental disorders. The Schizophrenia and Substance Use Disorders modules will be adopted for this project [50].

Drug Abuse Screening Tool

The Drug Abuse Screening Tool (DAST) will be used to track cannabis use indicative of abuse before clinic registration and at 12 months. The DAST monitors drug use problems during the previous 12-month period. The DAST identifies drug abuse when a score of 6 or more is obtained. The lowest score is 0, and the highest score is 20 [52]. It has been used in previous studies to identify substance use disorder among young people with a first episode of psychosis [16].

Insight

The Birchwood Insight Scale will be completed. It contains items about illness awareness, symptom recognition, and the need for treatment. It has been validated in schizophrenia and patients with a first episode of psychosis [53].

The Cannabis Experience Questionnaire has been used to measure the intoxication effects of cannabis among cannabis users and has been validated with confirmatory factor analysis [54]. It has been used in early phase psychosis to track the frequency and THC content of cannabis use [55]. It assesses the frequency of use (every day, more than once a week, about once a week, about once a month, a few times each year, only once or twice, and never) [55]. It has been used in epidemiological studies involving first-episode psychosis participants in the United Kingdom to estimate the type of cannabis used. This aspect was developed by collecting data on the THC content of cannabis confiscated by police [56]. We have adapted it for the Ontario context by estimating THC content based on a Marketplace survey of products sold at dispensaries in Canada [57,58]. It includes the following question: What potency of cannabis do you/did you usually buy? (Indicate the most frequent if this varies). The response options are (1) Low potency, 5% or less (THC content labeled or hash oil); (2) Medium potency, 6%-14% (THC content labeled at a government-sponsored dispensary); (3) High potency, 15%-29% (most dispensaries not licensed by the government); (4) Extremely high potency, 30%-100% (synthetics, concentrates, shatter, dab, or spice).

Analyses

Quantitative Analysis

Descriptive statistics (mean and standard deviation for normally distributed continuous variables, median for variables with skewed distribution, and frequency and percentage for categorical variables) will be used to depict the demographic and clinical characteristics and will explore the relationship between the variables of interest. Relevant tests of significance, including chi-square, correlation, and regression tests, will be performed.

Visit 2: Perspectives on Cannabis and Psychosis

Research Questions

The primary research questions about the perceptions of cannabis and psychosis are as follows: How do young people with a first episode of psychosis and cannabis use disorder from Black racialized communities conceptualize the mental health impacts of cannabis on psychosis? How do gender and ethnicity influence the messages?

Study Population and Recruitment

See Visit 1: Baseline Assessments for criteria and procedures. The same participants will take part in this phase of the study.

Data Collection

Qualitative Interview

The research staff will ask participants to share their stories and perspectives involving cannabis and psychosis. Semistructured open-ended questions will be used to elicit narratives on mental health and cannabis use experiences. Stories will also be elicited about the age of first use, frequency of use, potency of products, choice of products, route of administration, and views on how gender or ethnicity influences cannabis use.

The interviews will be recorded and transcribed verbatim. The Sex- and Gender-Based Analysis Plus will be used to ensure the data are collected and analyzed in a manner sensitive to gender (sociocultural) and to integrate factors, such as race, language, age, immigration, or disability [59]. The research staff will explore within-group themes that are contextually grounded in the following: (1) race and ethnicity as social constructs (for example, Black African versus Black Caribbean), (2) gender (men/transmen versus women/transwomen versus fluid/nonbinary/two-spirit), (3) immigration status (first or second generation), and (4) study site (for example, Montreal versus London to capture variations based on geography).

Qualitative Analysis

The data will be thematically analyzed as described by Braun and Clark [60]. The research staff will conduct thematic analysis, code and label data extracts, and search for phrases and imagery related to cannabis and psychosis, focusing on different perspectives based on gender and ethnicity. This analysis will be presented to the advisory council to help formulate meaning from the data and to help create visual models of the constructs.

Sample Size

Twelve or more participants from each of the 2 ethnic groups and the 2 largest gender groups should be sufficient to reach saturation of the perspectives for each group by the third visit. Saturation has been shown to occur within the first 12 interviews within a group [61].

Visit 3: Gameplay and Knowledge Transfer

Research Questions

The research questions are as follows: (1) How do the themes about cannabis and psychosis change after playing the Back to Reality Series? (2) What is the game's impact on knowledge acquisition about cannabis and psychosis?

Hypothesis

We hypothesize a significantly greater knowledge test score (>18%) in the group first exposed to the Back to Reality Series compared to the control game. We expect this finding for Black African and Black Caribbean groups, Black men, Black women, and all ethnic groups with a first episode of psychosis and cannabis use disorder.

Study Population and Recruitment

See Visit 1: Baseline Assessments for criteria and procedures. The same participants will take part in this phase of the study.

Study Design

This study phase involves quantitative and qualitative components to establish the feasibility of knowledge acquisition through gameplay involving the Back to Reality Series. Knowledge acquisition will be measured using scores on a quiz, and changes in insight will be gleaned from qualitative inquiry into changes in perceptions about cannabis and psychosis before and after playing the game.

Data Collection and Procedures

The video games will be streamed over Zoom by the research staff. Participants will be randomized to determine the gameplay order (either the Back to Reality Series or the control game will be played first). A software program embedded within the download of the Back to Reality Series randomly assigns the order in which each participant plays the first game on a 1:1 basis. The randomization is not to allocate participants into groups. The experimental and control games are packaged on the screen to protect the blinding at the outset. However, the video games are not associated with preconceived notions of therapeutic benefit, which minimizes bias. The video games are password protected, so participants will not have had prior access.

Subsequently, participants will complete a quiz measuring factual knowledge about the impact of cannabis on psychosis. Participants are randomized so that differences in quiz scores can be attributed to gameplay interventions, which is an advantage over pre-post gameplay designs for quantitative analysis. This process also avoids having participants complete the same or similar quiz twice in a day. The research staff will conduct the knowledge test by displaying the questions to the participants and reading out each item. After completing the quiz, participants will immediately play whichever game remains. Thus, if the participant was randomized to play the Back to Reality Series first, the control game, Morpheus' Spell, will subsequently be played. Each participant will complete a gameplay survey about the Back to Reality Series. Finally, participants will undergo a second qualitative interview to discuss ideas and impressions from their gameplay experiences and reflect upon their views about the relationship between cannabis and psychosis after playing the game.

Measures

PCT

The PCT Quiz assesses relevant knowledge about the relationship between cannabis and psychosis. It takes about 10 minutes to complete and involves 10 multiple-choice questions worth 1-point each, with scores ranging from 0 to 10. The researchers will read the questions aloud to reduce the impact of reading literacy. The details are described elsewhere regarding the development of the quiz, and its reliability and validity [42].

Postgameplay Survey

This survey explores the satisfaction with the gameplay experience. It was adapted from a randomized control study of video games designed to increase knowledge about antenatal care [62]. The items include "comfort with gameplay," as well as enjoyment of the game, graphics, music, and story. Each item is rated as "Yes" (1 point) or "No" (0 points). Additional questions include the frequency of video gameplay and the types of devices used to play video games. The survey has been piloted with the Back to Reality Series involving Black youth [42].

Data Collection

Gameplay, Quantitative Test, and Qualitative Inquiry

This section will take 60-120 minutes. Each participant will be provided with a link to download the set of video games. A software program will randomly assign the order in which each participant plays the first game, the Back to Reality Series, or the control game on a 1:1 basis. It takes 45 minutes in total to play all the video games. Subsequently, the research staff will conduct the PCT Quiz by displaying the questions to the participants and reading out each item. Finally, the participants will play whichever game they had not played first.

Qualitative Interview

After a short break, the research staff will conduct qualitative interviews about the gameplay experiences and the perceptions of the mental health effects of cannabis and psychosis after playing the game. The participants will share how the perceptions of their own personal experiences with psychosis and cannabis might be influenced by their gameplay experiences. Participants will be asked about their views on the main character's use of cannabis and their opinions about using video games for youth from Black communities.

Analyses

Qualitative Analysis

The same qualitative analysis and sample size procedures as outlined in Visit 2: Perspectives on Cannabis and Psychosis will be adopted for this analysis. However, the data sets from *Perspectives on Cannabis and Psychosis* and *Insight and Knowledge Acquisition* will be integrated during the analysis to detect changes in perception comparing pregame and postgame data sets to identify changes in insight or opinions. Triangulation of the feedback from different disaggregated racialized and gender groups will be performed to compare and contrast the views on cannabis and psychosis in order to identify relevant themes and ideas [63].

Quantitative Analysis

We will compare the performance of the groups on the PCT Quiz using the *t* test. A minimum difference of 18% in PCT Quiz scores represents a statistically and meaningfully significant increase in knowledge, based on a pilot study [45].

Sample Size

Based on pilot data involving 10 participants with a first episode of psychosis, the mean baseline score was 6.5 (SD 1.3). The effect size is 1.17 (18% × 6.5) to detect a difference of 18%. The standardized effect size (E/S) is 0.9 (1.17/1.3 [effect size/SD]). The power calculations [64] suggest that 20 participants are sufficient per group. With a minimum of 24 participants per gender and racialized group at visit 1, there would be at least 20 participants per group by visit 3 (up to 4 weeks later), with a projected dropout rate of 15%.

Results

We began recruiting participants for this study in September 2021. So far, we have had 2 advisory committee meetings, one in October 2021 and the second in December 2021. Recruitment

is being tailored to fit with the pandemic-related restrictions. The recruitment target is expected to be met by December 2022. Full analysis of the results will be completed subsequently.

Discussion

The anticipated findings for this study center around knowledge exchange about cannabis and psychosis, and engaging young people experiencing a first episode and, in particular, those of Black African and Caribbean descent. We expect the video games to encourage meaningful discussions about cannabis and psychosis. We hope the characters, narrative, interactivity, and video gameplay promote retention and engagement. The PCT Quiz will verify knowledge acquisition. Attitudes and satisfaction will be documented by qualitatively analyzing themes reviewed by the advisory council. The Back to Reality Series, combined with tutorials led by university students, has been shown in a pilot study involving healthy participants to be enjoyable and to transfer knowledge about cannabis and psychosis to youth from Black communities [42].

The strength of this protocol includes community engagement provided by the advisory council, which promotes research priorities and interpretations that are more acceptable to youth with serious mental illness and young people from Black communities. A limitation of the design includes the lack of follow-up to document the long-term impact of the games.

Few Canadian studies report cannabis use based on race or ethnic groups; nevertheless, ethnic differences have been found between young people of Black African background and those of Black Caribbean background, with the latter group more likely to report problematic use [23]. Studies conducted in the United States involving healthy populations have shown that Black youth are more likely than White youth to report self-medicating with cannabis to relieve physiological symptoms associated with anxiety [65]. However, many studies suggest that youth use cannabis because they believe it will alleviate anxiety symptoms regardless of race, but no studies to date indicate that youth self-medicate to ease psychosis symptoms [66,67]. This study is unique because it will explore the intersections of race, ethnicity, and cannabis use among young people experiencing their first episode of psychosis.

Future directions include using digital video games as psychoeducational products that explore credible scientific knowledge about the risks and benefits of cannabis use. The video games provide a unique opportunity to reach young people from Black communities with the help of community partners. The Back to Reality Series could offer a coherent knowledge transfer strategy for education and engagement. Moreover, the Back to Reality Series could become a sustainable evidence-based online knowledge translation product, reaching an appropriate audience through networks connected to early interventions in psychosis and community agencies. Validation of the psychoeducational value of the Back to Reality Series could support future studies examining its ability to promote readiness for change and its ability to improve not only insight but also engagement with cannabis use disorder treatments offered by early intervention programs.

Conflicts of Interest

SA was involved in the development of the Back to Reality Series. LP reports personal fees from Janssen Canada, Otsuka Canada, SPMM Course Limited, UK, and Canadian Psychiatric Association; book royalties from Oxford University Press; and investigator-initiated educational grants from Janssen Canada, Sunovion, and Otsuka Canada outside the submitted work in the last 5 years. MF was involved in the development of the Back to Reality Series and is leading the creation of the French version of the video game.

Multimedia Appendix 1
CIHR peer review.
[PDF File (Adobe PDF File), 431 KB - resprot_v11i5e36758_app1.pdf]

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Abbreviations

CBT: cognitive behavioral therapy
DART: Diagnostic Assessment Research Tool
DAST: Drug Abuse Screening Tool
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

PCT: Psychosis and Cannabis Test
THC: delta-9-tetrahydrocannabinol

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Protocol

Developing Reporting Guidelines for Social Media Research (RESOME) by Using a Modified Delphi Method: Protocol for Guideline Development

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Abstract

Background: Social media platforms, such as Facebook, Twitter, and Instagram, are being increasingly used to deliver public health interventions. Despite the high level of research interest, there is no consensus or guidance on how to report on social media interventions. Reporting guidelines that incorporate elements from behavior change theories and social media engagement frameworks could foster more robust evaluations that capture outcomes that have an impact on behavior change and engagement.

Objective: The aim of this project is to develop, publish, and promote a list of items for our Reporting Guidelines for Social Media Research (RESOME) checklist.

Methods: RESOME will be developed by using a modified Delphi approach wherein 2 rounds of questionnaires will be sent to experts and stakeholders. The questionnaires will ask them to rate their agreement with a series of statements until a level of consensus is reached. This will be followed by a web-based consensus meeting to finalize the reporting guidelines. After the consensus meeting, the reporting guidelines will be published in the form of a paper outlining the need for the new guidelines and how the guidelines were developed, along with the finalized checklist for reporting. Prior to publication, the guidelines will be piloted to check for understanding and simplify the language used, if necessary.

Results: The first draft of RESOME has been developed. Round 1 of the Delphi survey took place between July and December 2021. Round 2 is due to take place in February 2022, and the web-based consensus meeting will be scheduled for the spring of 2022.

Conclusions: Developing RESOME has the potential to contribute to improved reporting, and such guidelines will make it easier to assess the effectiveness of social media interventions. Future work will be needed to evaluate our guidelines' usefulness and practicality.

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KEYWORDS

social media; research design; web-based social networking; health behavior; health promotion; public health

Introduction

Social media use is becoming increasingly common; social media has been estimated to be used by more than half of the world's population [1,2]. Given social media's potential for promoting widespread public engagement, it is commonly incorporated into public health interventions [3,4]. The term *intervention* in this protocol refers to a spectrum of activities that range from national awareness-raising public health campaigns, such as awareness months, to more targeted activities that use social media groups to deliver information or interventions to specific audiences [5,6].

Systematic reviews of public health interventions involving social media have shown that social media has been used for a wide range of health promotion activities, such as weight management improvement, physical activity, smoking cessation, mental health improvement, the promotion of the use of health care services, HIV prevention, cancer prevention, and vaccination uptake [7-18]. These reviews highlight several potential benefits of social media interventions; they are generally found to be acceptable and feasible, and they offer unique advantages over traditional health messaging, such as the functionality of targeting information regarding specific populations, particularly those who may be hesitant to access in-person services [10,14,19,20].

Several methodological challenges however have been identified that hinder the ability to draw strong conclusions about the effectiveness of social media interventions. For example, some studies do not sufficiently describe interventions to allow for replicability, to understand the "active ingredients" of an intervention, or to understand the behavior change techniques used [11,13,15,16]. Very few studies explore the impacts on behavior change or quantitative clinical outcomes, and the majority instead focus on descriptions of engagement within a social media platform, such as views or shares, which may not indicate a genuine increase in knowledge or change in behavior [8,10,11,15,17]. Further, 3 systematic reviews reported that the majority of their included studies had a high or unclear risk of bias, which prevented a meta-analysis from being performed [8,13,21]. Many campaigns are not formally evaluated, and reports on social media campaigns are often not publicly available. These issues further contribute to the challenge of synthesizing research evidence. Furthermore, although social media interventions have been carried out in a variety of different populations, there are very few studies that actively explore and report the impact of social media interventions on health inequalities [7,11,22].

There are existing reporting guidelines that have some relevance to social media interventions, such as Criteria for Reporting the Development and Evaluation of Complex Interventions in Healthcare: Revised Guideline (CReDECI 2) for complex health care interventions, CONSORT (Consolidated Standards of Reporting Trials) for randomized controlled trials, Guidance for Reporting Intervention Development Studies in Health Research (GUIDED) for intervention development, and guidelines for using the theory of change to design and evaluate public health interventions and for better reporting on interventions (eg, Template for Intervention Description and Replication [TIDieR]) [23-27]. However, there are currently no reporting guidelines available that take into account the diverse and unique aspects of research on social media interventions. For example, not all evaluations of social media interventions have the same study design; it is not always feasible or possible to randomize participants in a trial, and some studies are observational in nature (eg, an evaluation of a national awareness campaign delivered by a third party) [19,20,28].

There is therefore a clear need for guidance to be developed on the reporting of social media interventions. The development of reporting guidelines that incorporate elements from existing and widely used behavior change theories and social media engagement frameworks could foster more robust evaluations that capture outcomes that have an impact on behavior change and engagement and inform policy decisions [19,29,30]. Specific guidelines for social media research could include additional domains about the methods for collecting data, provide technical information about social media platforms and the social context in which the research takes place, and address the ethical and privacy issues that are unique to social media research.

The aim of this project is to develop and establish consensus on which items should be included in reporting guidelines for social media interventions. The development of these guidelines will be achieved by conducting a series of Delphi surveys to achieve consensus on which items should be included.

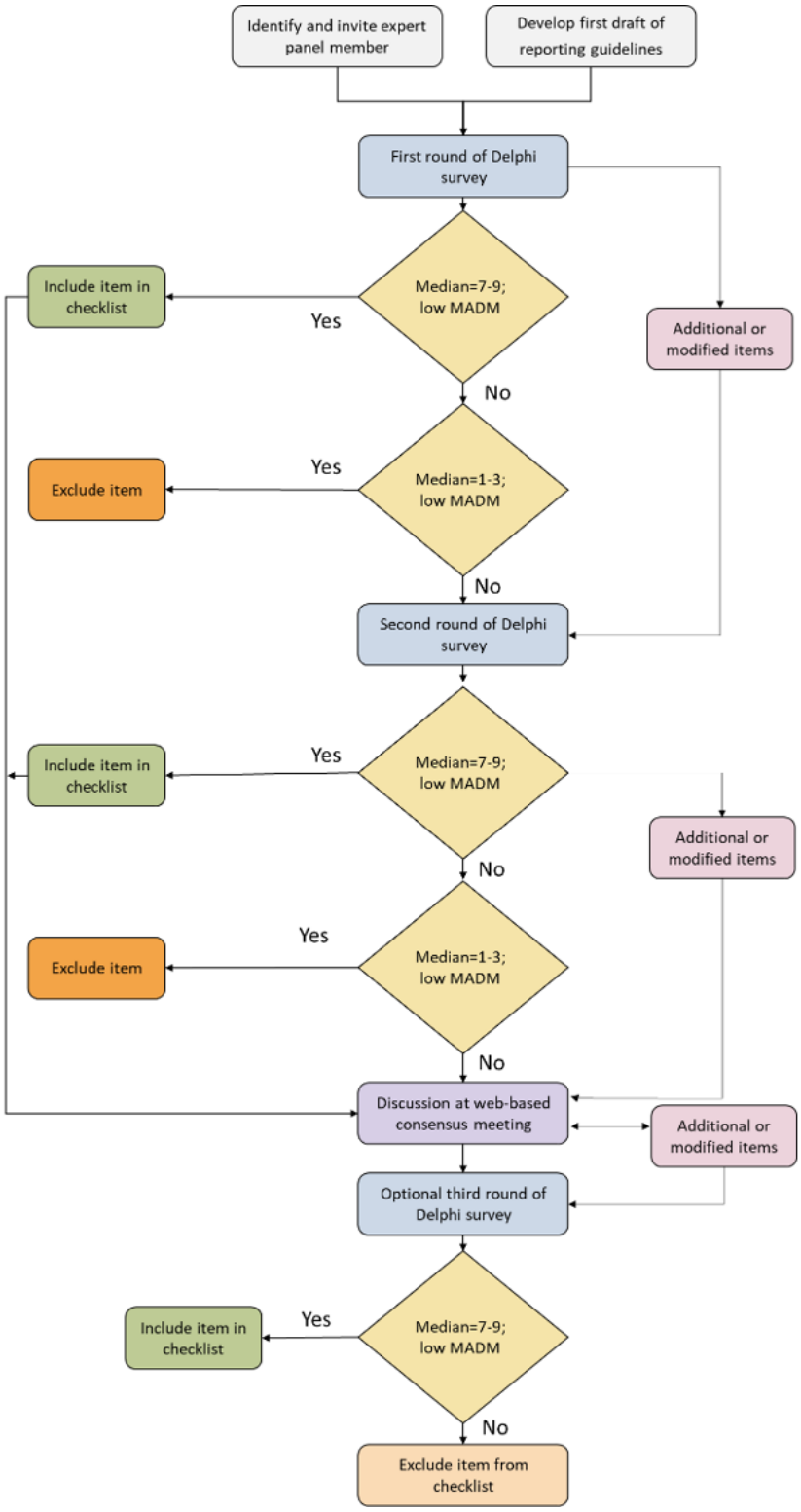
Methods

The methods that will be used in this project have been informed by guidance on the development of reporting guidelines that was produced by Moher et al [31] in 2010 and the EQUATOR (Enhancing the Quality and Transparency of Health Research) Network [32]. The development of our Reporting Guidelines for Social Media Research (RESOME) has been registered on the EQUATOR Network website [33].

Design

The reporting guidelines will be developed by conducting a Delphi exercise, during which several rounds of questionnaires will be sent to experts and stakeholders. The questionnaires will ask them to rate their agreement with a series of statements until a level of consensus is reached. This will be followed by a web-based consensus meeting to finalize the reporting guidelines [34,35]. Figure 1 summarizes the processes of the Delphi method.

Figure 1. Delphi process flowchart. MADM: mean absolute deviation from the median.



The project is led by an expert, multidisciplinary executive panel composed of 9 people from the fields of behavioral science, epidemiology, health services research, public health, social media, and statistics and patient and public representatives. The panel is responsible for providing academic oversight for the project and directly participating in some aspects of the research activities, such as identifying participants, chairing discussions, and contributing to developing research reports.

Participants

As recommended by the EQUATOR Network [32] and the guidance produced by Moher et al [31] in 2010, stakeholders with expertise in statistics, epidemiology, and research methodology; primary care and public health professionals; journal editors; and patient and public representatives will be invited to form an expert panel in addition to researchers with experience in conducting or evaluating social media interventions. Potential participants will be identified via

research networks and invited to take part by email. We will contact social media researchers and journal editors directly and advertise the project on social media. The invitation email will contain background information on the project; a link to the preprint of the protocol; a participant information sheet; and a privacy notice stating that any personal data will be collected, stored, and deleted in accordance with the UK General Data Protection Regulation (2018) [36]. Potential participants will be asked to share information about the project with colleagues and among their own research networks to increase the pool of potential participants. The final participant panel will include a maximum of 30 people. We will aim to ensure that the panel is diverse with respect to age, gender, ethnicity, and subject specialty.

Delphi Survey

The purpose of the Delphi exercise is to generate a list of items for consideration at the consensus meeting [34]. The first iteration of the checklist items was developed based on previously conducted research and relevant guidelines. The current items are outlined in Table 1 [4,11,23-25]. Using questionnaires will allow for anonymous responses, which can help with avoiding influence from other members, and allow people from geographically dispersed countries to participate. The purpose of the web-based consensus meeting is to provide an opportunity for clarifying and discussing items.

Participants will be asked to rate their agreement with including each item on a scale of 1 to 9 (1=strongly disagree; 9=strongly agree). Each question will be accompanied by a free-text box, in which participants will be able to add comments, such as justifications for their responses, suggestions for alternative phrasing, or additional items.

After the first round, items for which there is consensus for inclusion will be retained (see *Statistical Analysis* section for further details). Each participant will receive the aggregate results of the survey, along with their own answers to the questions. Any items for which consensus is not reached will be included in a second round of surveys, along with any additional items or modifications identified through free-text responses. Participants will then be presented with the results of the first round and asked to rate the items again before the web-based consensus meeting.

Table 1. The draft of Reporting Guidelines for Social Media Research to be included in round 1 of the Delphi exercise.

Sections and item numbers	Description[a]
Title and abstract	
1A	Indicate the use of social media in the title or abstract
1B	Indicate the social media platform(s) in the title or abstract
Methods: study design	
2A	Specify study design e.g., observational, experimental, qualitative
2B	Specify if this study reports an evaluation of an existing social media campaign (e.g., a process evaluation) or a novel intervention
2C	Specify the trial registration details and/or previously published protocol, if applicable
Methods: participants and data	
3A	Describe the eligibility criteria for participants to be involved in the study or the population targeted by the intervention
3B	Describe any methods used to identify participants
3C	Describe how participants were recruited into the study
3D	Explain if the data are publicly available and where it can be accessed
3E	Describe the methods used to collect data e.g., search terms, social media metrics or data mining
Methods: setting	
4A	Provide a summary of the social media platform(s), including the main features and how it is used
4B	Provide information about the number of users of the social media platform(s) and their characteristics
4C	Describe any relevant algorithms employed by the social media platform(s) at the time of the research which may have an impact on the way that information is shared and viewed
4D	Provide details of any social, political and economic contextual factors relevant to the project e.g., ongoing public debates or events
4E	Provide dates of exposure, follow-up, and data collection
Methods: intervention	
5A	Describe the primary and secondary aims of the intervention or campaign (e.g., change in knowledge, awareness, intentions, behaviours, or health outcomes)
5B	Describe how the social media intervention or campaign works with reference to behaviour change techniques, mechanisms of action, and targeted behaviour change
5C	State whether the intervention or campaign was paid for or not
5D	Describe the purchase model if used for any advertisements or promoted posts
5E	Describe the implementation strategy for the social media campaign and any incentives for participants
5F	Describe the resources required for the campaign or intervention e.g., time, money, technology, equipment, and partners
5G	Provide a description of the intervention with sufficient detail to allow replication, including any links to audio/visual materials
5H	Specify whether the intervention materials are subject to a copyright license or can be reused e.g., through a public or creative common license
5I	Describe the creative process underlying the development of intervention materials, including an acknowledgement of any outside agencies involved in developing creative materials
5J	Describe any aspects of the intervention which took place outside of social media e.g., television, print and radio communications
5K	Describe any secondary features of the intervention or campaign which may impact the outcome measures e.g., sponsors, collaborators and links to other websites
Methods: measures	
6A	Reach: Describe the demographic data of included participants, if applicable

Sections and item numbers	Description[a]
6B	Low-medium level engagement: Describe which measures were used to measure engagement with the intervention e.g., likes, comments, reposts
6C	High-level engagement: Describe any measures for change in knowledge, awareness of offline activities e.g., measures of behaviour change, intentions, or health-related outcomes.
Methods: ethics	
7A	Provide details of any ethical implications related to consent, privacy issues and data protection
7B	Provide details of any safeguarding measures e.g., moderation of discussion
7C	Describe any commercial interests related to the project e.g., funding, sponsorship, advertisements, endorsements
7D	Describe how any commercial interests were communicated to participants
Results: participant flow diagram	
8	Include a flow-diagram showing the number of people who were targeted, exposed to the intervention, engaged with the intervention, and included in the analysis, if applicable
Results: participant characteristics	
9	Include a table showing demographic information for participation (by group if a control group is used), if applicable
Results: outcomes	
10A	Report descriptive statistics of social media metrics, such as reach, views, likes and reposts
10B	Include a description of novel content such a conversations, videos, or images
10C	For measures of high-level engagement, provide an estimation of differences between groups or over time with a measure of precision (such as 95% confidence interval).
Discussion: summary of results	
11	Describe the main results in the context of the objectives described in the methods section and any previously published research protocols or trial registrations
Discussion: feasibility	
12	Discuss the feasibility of the campaign and intervention for wider implementation with reference to the benefits in relation to the resources required
Discussion: generalizability	
13	Discuss which components are generalisable to other social media platforms and contexts e.g., for different target behaviours, socio-demographic groups or countries

[a]All descriptions appear exactly as they did when they were presented to participants.

Consensus Meeting

In-person meetings are one of the major challenges of consensus meetings due to the cost and practicality of convening an international group of experts. Due to the ongoing COVID-19 pandemic, these meetings will be conducted on the internet, which will eliminate the cost of international travel and allow for the greater participation of experts in different countries.

The consensus meeting will be limited to 30 people to allow for effective communication and participation and will take place over 1 day. Prior to the meeting, preparations will be made, including developing the agenda and presentations relevant to the session; making sure that participants have information about joining the session; sharing the results of the Delphi exercise; and sharing any other relevant materials, such as the current item list. The meeting will be conducted by using web-based conferencing software, such as Zoom (Zoom Video Communications Inc) or Remo (Remo.co), and conversations will be recorded for future reference.

The consensus meeting will include presentations on the research background and the results of the Delphi exercise. Each item will be discussed in turn to allow participants to express their viewpoints in more detail and to ultimately reach consensus on items' inclusion or exclusion in the reporting guidelines. Due to the meeting taking place on the internet, it will be possible to incorporate live and anonymous voting on items to break deadlocks. The meeting will also be used to discuss additional reporting guidelines, such as the inclusion of a participant flowchart or a summary of social media metrics; the name of the reporting guidelines; the publication and dissemination strategy; and the accompanying explanation and elaboration document.

Statistical Analysis

For each item, the mean, SD, median, IQR, and mean absolute deviation from the median (MADM) will be used to assess the strength and extent of agreement [37]. Medians of 7 to 9 will be defined as strong support, medians of 4 to 6 will be defined as moderate support, and medians of 1 to 3 will be defined as

no support. The MADM will be categorized as high (>2.68), medium (1.34-2.67), or low (<1.33), with a low MADM representing a high-level consensus. Items will be included if the median score is ≥7 and the MADM is low (<1.33). Items will be excluded if the median score is ≤3 and the MADM is low (<1.33). Items that do not meet these criteria after the second round will be discussed in the web-based consensus meeting, and an additional, third Delphi round will be conducted after the meeting. If consensus is not reached by this stage, a decision will made by the executive panel.

Free-text comments from each Delphi survey will be qualitatively analyzed by using a thematic analysis [38]. The main themes will be reported to the executive panel and the participants in order to identify any additional items or item modifications that need to be included in the next round of the survey.

Developing the Reporting Guidelines and an Explanatory Document

After the consensus meeting, the reporting guidelines will be published in the form of a paper outlining the need for the new guidelines and how the guidelines were developed, along with the finalized checklist for reporting. Prior to publication, guidelines will be piloted to check for understanding and to simplify the language, if necessary.

An explanation and elaboration document will be published alongside the reporting guidelines. The document will explain why each reporting guideline is important and provide examples for each item.

Ethics Approval

Ethical approval was obtained in June 2021 from the University College London ethics committee (ID number: 14687/004) to contact participants and to collect and store their responses in accordance with the UK General Data Protection Regulation (2018). All participants will complete a web-based consent form prior to taking part in the study and have the right to withdraw themselves from the study.

Dissemination

After the publication of the reporting guidelines, a range of strategies will be implemented to improve the usability and implementation of the reporting guidelines (Textbox 1).

Textbox 1. Strategies for improving the usability and implementation of Reporting Guidelines for Social Media Research.

Strategies

- Ensuring that the guidelines are freely available and are in an editable format
- Creating a dedicated website containing additional resources
- Recording the guidelines on the EQUATOR (Enhancing the Quality and Transparency of Health Research) Network database
- Obtaining journal endorsement and endorsement from other organizations
- Presenting the guidelines at relevant conferences and meetings
- Writing blog posts and other social media posts about the guidelines
- Developing and delivering web-based training in using the guidelines
- Translating the guidelines into different languages

Results

As of January 2021, the executive panel has been convened and has drafted the first version of the RESOME checklist. The recruitment of participants and round 1 of the Delphi survey took place between July and December 2021. Round 2 is due to take place in February 2022, and the web-based consensus meeting will be scheduled for the spring of 2022. The finalized guidance and supporting explanatory document will be published by August 2022.

Discussion

Study Implications

Social media interventions are a relatively recent phenomenon that has attracted a high level of research interest; however, there is a clear need for reporting, as evidenced by the large number of reviews that report a lack of robust and rigorously conducted studies [8,10,11,13,15-17,21]. The rapid changes in the way that people use social media make investigating methods for promoting the public's engagement with health messages via social media a high priority. The development of and adherence to reporting guidelines for social media interventions will facilitate replicability and allow for a better understanding of which interventions are effective and for whom they are effective.

Delphi surveys are a validated consensus method that involve using anonymous surveys to quantify levels of consensus according to an a priori statistical analysis plan. This approach is especially beneficial because it allows for the equal contribution of participants and prevents dominating personalities from impacting decision-making [39]. Qualitative and quantitative data will be analyzed to achieve a deeper understanding of participants' responses. The main limitation of Delphi surveys is the lack of opportunities for nuanced discussions or clarifications among individuals. This limitation will be addressed with an interactive and deliberative consensus meeting. Due to the web-based nature of the consensus building process, a broader range of stakeholders than what would normally be possible will be recruited. By including participants from different geographical regions who would not normally be able to participate, it is possible to achieve a global

perspective and an increased level of diversity in terms of participants [40]. The publication of this protocol provides an opportunity to improve the research methods (via feedback from reviewers) and transparency for the process of including and excluding items.

Limitations

There are some limitations to this project that must be acknowledged. First, the recruitment of the expert panel may be challenging in terms of finding and engaging people with relevant expertise and diverse opinions. Second, the reporting guidelines that will be produced in this project may not be applicable or relevant to all types of social media interventions. It is expected that these social media reporting guidelines could and should be used by researchers in conjunction with other existing reporting guidelines (eg, CReDECI 2, CONSORT, GUIDED, and TIDieR) [23-27]. Third, the field of social media research is fast-moving, and as such, any reporting guidelines will require regular reviews and updates to reflect changes in methodological approaches. Finally, once the reporting guidelines have been published, several steps will be taken to disseminate and encourage their use. However, this will require engagement and endorsement by relevant journals and third-party organizations.

Conclusions

There is a lack of high-quality research on social media interventions, which limits our understanding of their effectiveness. This protocol outlines the methods that will be used to develop reporting guidelines for social media interventions. The development of these guidelines are a first step toward improving the quality, rigor, and robustness of social media interventions. Future work will be needed to evaluate the guidelines' usefulness and practicality.

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Authors' Contributions

AK and CVW conceptualized the project. All authors contributed to refining the study methodology and contributed meaningfully to the drafting and writing of the final protocol.

Conflicts of Interest

None declared.

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
CReDECI 2: Criteria for Reporting the Development and Evaluation of Complex Interventions in Healthcare: Revised Guideline
EQUATOR: Enhancing the Quality and Transparency of Health Research
GUIDED: Guidance for Reporting Intervention Development Studies in Health Research
MADM: mean absolute deviation from the median
NIHR: National Institute for Health Research
RESOME: Reporting Guidelines for Social Media Research
TIDieR: Template for Intervention Description and Replication

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Protocol

Natural Language Processing to Identify Digital Learning Tools in Postgraduate Family Medicine: Protocol for a Scoping Review

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Abstract

Background: The COVID-19 pandemic has highlighted the growing need for digital learning tools in postgraduate family medicine training. Family medicine departments must understand and recognize the use and effectiveness of digital tools in order to integrate them into curricula and develop effective learning tools that fill gaps and meet the learning needs of trainees.

Objective: This scoping review will aim to explore and organize the breadth of knowledge regarding digital learning tools in family medicine training.

Methods: This scoping review follows the 6 stages of the methodological framework outlined first by Arksey and O'Malley, then refined by Levac et al, including a search of published academic literature in 6 databases (MEDLINE, ERIC, Education Source, Embase, Scopus, and Web of Science) and gray literature. Following title and abstract and full text screening, characteristics and main findings of the included studies and resources will be tabulated and summarized. Thematic analysis and natural language processing (NLP) will be conducted in parallel using a 9-step approach to identify common themes and synthesize the literature. Additionally, NLP will be employed for bibliometric and scientometric analysis of the identified literature.

Results: The search strategy has been developed and launched. As of October 2021, we have completed stages 1, 2, and 3 of the scoping review. We identified 132 studies for inclusion through the academic literature search and 127 relevant studies in the gray literature search. Further refinement of the eligibility criteria and data extraction has been ongoing since September 2021.

Conclusions: In this scoping review, we will identify and consolidate information and evidence related to the use and effectiveness of existing digital learning tools in postgraduate family medicine training. Our findings will improve the understanding of the current landscape of digital learning tools, which will be of great value to educators and trainees interested in using existing tools, innovators looking to design digital learning tools that meet current needs, and researchers involved in the study of digital tools.

Trial Registration: OSF Registries osf.io/wju4k; https://osf.io/wju4k

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KEYWORDS

digital learning tools; medical education; primary care; digital learning; scoping review; family medicine; bibliometric; scientometric; natural language processing; e-learning; medical curriculum; medical curricula; medical school

Introduction

Background

The onset of the COVID-19 pandemic and subsequent rapid transition to distance learning have highlighted the growing need for digital learning tools [1], which include any electronic application, game, or resource that supports education [2,3]. In this study, "digital learning tools" refers to any online or offline computer-based resource, mobile app, electronic game, or resource that supports, enhances, or contributes to medical education. Students currently enrolled in postsecondary education programs are familiar with technology and eager to utilize such tools to support their education. The growing demand for these tools reflects the current preference by students for digital tools to acquire and consolidate information [4].

Digital learning tools boast a variety of benefits, including enhanced learning with fewer resources, increased levels of feedback, and more detailed assessments, making them an effective resource for learners looking to meet the challenges of medical education in a digital age [5]. Previous literature reviews have been conducted on digital learning tools in the education of health professionals [6-18]. However, little research has been done to explore what digital learning tools are currently available for postgraduate family medicine training. This scoping review will provide an overview of research activities relating to the development and use of digital learning tools in this discipline. These results could promote broader use of existing tools and help identify gaps that would inform research and development of new tools for family medicine training. The information generated from this type of review is particularly valuable in family medicine, because this field is a broad-based clinical discipline facing the unique challenges of increasing the efficiency of training, meeting increased demands for social accountability, addressing the shift toward competency-based education, and keeping up with continuous advances in medical education [19,20].

As postgraduate family medicine training evolves, it is critical to understand where and how digital learning tools are being developed, as well as how learners use and perceive them, to design validated frameworks for the development of such tools. To this end, our team is conducting a scoping review to explore, organize, and understand the breadth of knowledge regarding digital learning tools in family medicine training. To do this, we will utilize the scoping review methodology outlined by Arksey and O'Malley [21] and Levac et al [22], supplemented by natural language processing (NLP) techniques, to analyze the content and semantic structure of the included resources and perform social network analysis of their citations [23].

Objectives

This scoping review has three major objectives: (1) identify existing digital learning tools in postgraduate family medicine training; (2) identify and compare common themes and content areas across various studies emerging from thematic analysis and NLP techniques; and (3) identify coauthorship networks in the review's field of research to understand what resources are informing tool development.

These objectives align with the scoping review methodology. Specifically, a scoping review is useful for mapping fields with a wide and diverse range of material, and is an effective mechanism for presenting research findings to knowledge users. The NLP techniques will serve to supplement and enrich the thematic analysis, while the social network analysis will lay foundational knowledge about scientific collaboration in postgraduate family medicine digital tool research.

Novelty

Several previous literature reviews have evaluated the use of gamification and serious games (ie, games used primarily for instruction or building skills, rather than amusement) and other types of digital learning tools in medical education [6-18]. Many of these reviews have aimed to compare specific types of digital learning tools to traditional forms of education, summarizing the findings from randomized controlled trials (RCTs). The current scoping review will identify and consolidate information about all digital learning tools, including serious games, web-based resources, mobile apps, and social media platforms. This review will also include all publication types and gray literature. Since many new tools have not yet undergone formal evaluation processes through RCTs, a search of studies beyond RCTs is vital to capturing a complete picture of available tools and evidence related to their development, implementation, and use. Furthermore, this study will focus specifically on tools used in postgraduate family medicine education and identify gaps in the development and use of digital learning tools in this broad-based area of medical training.

Additionally, high levels of heterogeneity found in other studies that examined specific disciplines or specific digital tools suggest the need for a scoping review in order to describe and classify the types of available digital learning tools, identify key concepts and definitions in the literature, and map various types of evidence [8,11,12].

Finally, our scoping review will utilize artificial intelligence to organize the structure and content of the identified literature in novel ways. NLP is a type of artificial intelligence that uses machine learning algorithms to process large volumes of text effectively and is used in semantic analysis, machine understanding, clustering, and classification [24]. Previous studies have utilized NLP to reduce the burden of the literature review process by automating the identification and selection of latent topics in papers [25-29]. Such studies have used clustering methods to organize literature by similar topics and to describe and group research activities into common themes to complement classification performed by humans [26]. As

NLP develops, it may play an increasingly important role in accelerating and enhancing literature reviews.

In this study, we will use NLP techniques to assist with and supplement the data synthesis phase of the scoping review, specifically to identify common themes and content areas across various studies. Additionally, we will perform social network analysis—a technique that has been applied in diverse fields, including medical parasitology, information science, and information visualization [30-32]. We will use this analysis to examine information from chosen texts and resources to identify coauthorship and collaboration networks in the research and development of digital tools in family medicine training. By using these computational and NLP techniques, we will be able to identify major research topics and concepts and strategically recognize future directions of research and development in family medicine training.

The scoping review methodology, supported by NLP techniques, will allow us to identify and consolidate information related to existing digital learning tools in postgraduate family medicine training. This paper describes the process our team will take to identify relevant literature and collaborative networks that can be leveraged in future initiatives to design and implement digital learning tools in postgraduate family medicine training.

Methods

Ethics Approval

This scoping review does not involve human participants and, as such, does not require ethics approval according to the Ottawa Health Science Network Research Ethics Board. The study was registered with the OSF Registries (osf.io/wju4k).

Design

Our approach is informed by Arksey and O'Malley's [21] methodological framework for conducting scoping reviews, which has subsequently been enhanced by Levac et al [22]. This approach facilitates a systematic process for developing a research question, searching academic databases, screening results from these searches, extracting data from relevant studies, and collating the results for dissemination. We will engage and involve stakeholders throughout the entire project, as evidence suggests that public engagement can enhance reviews and make the results more useful [22,33]. We will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines [34]. Upon completing the selection of relevant articles and sources of evidence, the proposed NLP implementation will commence.

Stage 1: Identifying the Research Question

The following research question was developed through an iterative process involving discussions with the research team and knowledge users, including clinicians, medical educators, digital learning tool developers, and students: What digital learning tools exist for postgraduate family medicine training? The study development process was informed by both the lived experience of knowledge users and findings from a preliminary nonsystematic search of the literature conducted in the summer of 2020. The nonsystematic search aimed to find evidence on digital learning tools being used in postgraduate family medicine training. Due to the heterogeneity of the literature, we concluded that a scoping review would be necessary to understand what tools were being used.

Stage 2: Identifying Relevant Studies

The search strategy was developed in consultation with knowledge users and a health sciences librarian at the University of Ottawa.

Academic Literature Search

We conducted a search of 6 academic databases, including MEDLINE, ERIC (Education Resources Information Centre), Education Source, Embase, Scopus, and Web of Science, to identify literature that describes the use of digital learning tools in postgraduate family medicine training. The major concepts that defined subject heading terms and keywords were "family medicine training" and "digital learning tools" (Multimedia Appendix 1). MEDLINE, ERIC, Education Source, and Embase were searched using subject heading terms and keywords. Scopus and Web of Science were searched using only keywords, as these databases do not use subject headings. The search was built in MEDLINE and was then translated to be run in the other databases (Multimedia Appendix 2). The results of the academic literature searches were imported into Covidence software for deduplication and screening.

Gray Literature Search

The gray literature was searched with Google (Google LLC) to identify resources from university program websites, medical forums, and conference websites, in addition to searching for theses and dissertations. We used keywords identified in the academic literature search for the gray literature search (Multimedia Appendix 3). The search was limited to the first 10 pages of results. An advanced Google search was also used to identify relevant resources from university websites, family medicine organizations, medical school and residency organizations, and relevant conferences. The advanced search was also limited to the first 10 pages of results. The reference lists of the included articles were reviewed for additional literature relevant to our study. We did not review the reference lists of the articles found by searching the reference lists.

Stage 3: Selecting Studies

The third stage of the scoping review was study selection, which included an initial title and abstract screening, followed by full text screening.

Inclusion and Exclusion Criteria

Studies were considered for inclusion if they described the design, development, implementation, or evaluation of any type of digital learning tool used for postgraduate family medicine training. We included studies of all publication types and from all countries. We excluded articles that were not written in English or French and that were published before 2010. The year 2010 was chosen as a limit because we are interested in existing or emerging technologies such as virtual reality and artificial intelligence that are presently being used in family medicine education. Given the rapid and continuous advancements in the use of technology in education, evaluations

conducted before 2010 would not provide a strong indication of current technology. Moreover, a systematic review of virtual reality for the education of health professionals identified only 1 reference published before 2010 [17]. Thus, we do not expect that this choice will lead us to exclude many resources.

Since there exists a gap in the current literature examining the landscape of digital learning tools for postgraduate family medicine education, we decided to use a broad search strategy with limited exclusion criteria. However, this is an iterative process, and as such, more specific exclusion criteria will be discussed and added as we familiarize ourselves with the literature.

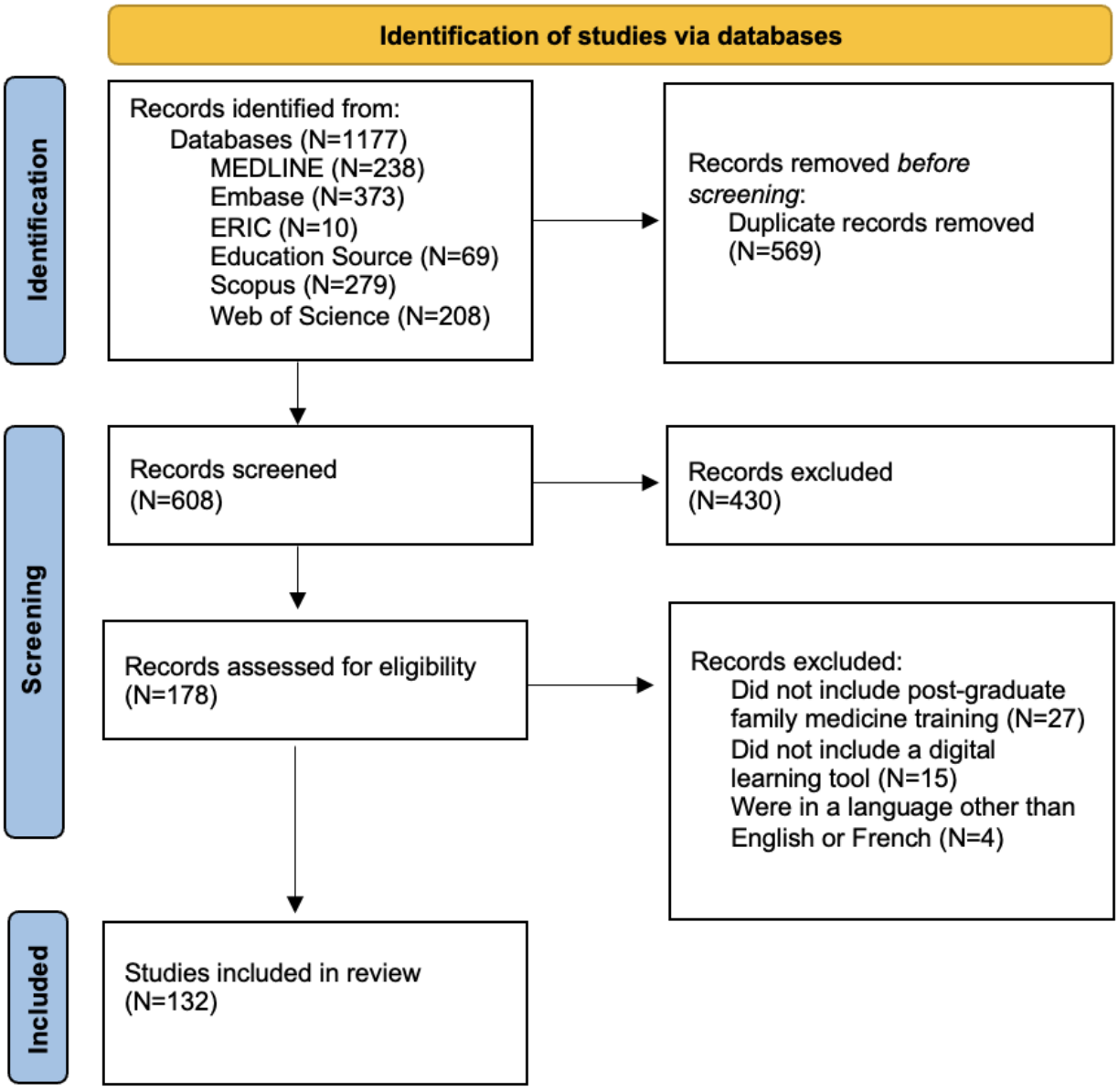
Title and Abstract Screening (Academic Literature)

Independent screening of the title and abstract of each article was performed by 2 reviewers based on the inclusion and exclusion criteria. If either reviewer included an article, it underwent full text screening. Additionally, if eligibility was unclear based on the information in the abstract, the article underwent full text screening.

Full Text Screening (Academic Literature)

Independent screening of each of the full texts identified for inclusion was performed by 2 reviewers, who discussed any disagreements. If an agreement could not be reached, a third person was consulted. The reasons for excluding studies were documented. A PRISMA-ScR flowchart that outlines the search decision process and the number of studies included at each phase of the process has been prepared (Figure 1) and will be disseminated in the paper describing the completed review.

Figure 1. PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) flowchart.



Gray Literature Screening

Gray literature was screened by 1 reviewer. Relevant articles and resources were recorded.

Stage 4: Charting the Data

Data will be independently extracted by 2 reviewers from the included articles and input into a data charting form. Data will include (as applicable) the title, author or authors, publication year, study objective, study design, country, description of the digital learning tool or tools, intervention description, study population, outcome measure or measures, and main findings. Charting is an iterative process, and therefore the data charting table may evolve as we familiarize ourselves with the literature. Data extraction elements may be further refined by our stakeholders, including knowledge users.

Stage 5: Collating and Reporting the Results

Characteristics and findings from all included literature will be tabulated and summarized. Aggregate data will also be presented. We will conduct a manual thematic analysis of the included studies to highlight key themes emerging from the literature.

In parallel with the manual data extraction and analysis processes, NLP techniques will be used to process the text corpus and identify common themes in selected articles. The NLP experiments will follow a 9-step process (Textbox 1) and will be grounded in several key approaches and techniques. This is intended as an approach to supporting manual data analysis.

Rahgozar and Inkpen [35,36] have shown that NLP algorithms, such as text clustering and classification, can produce useful results from less than 500 documents with an average of 10 lines each. This supports the feasibility of conducting NLP analyses on a reduced volume of texts after the selection of relevant articles and sources of evidence has been completed. A postdoctoral fellow with experience in applying machine learning in family medicine research has designed and will perform all analyses. Textbox 1 shows the sequence of steps that will be used, and we will henceforth refer to it to when describing our NLP procedure. First, the included articles will be organized (ie, corpus development) and will undergo text preprocessing (ie, tokenization, removing stop words, and clearing images) to facilitate subsequent NLP experiments (steps 1 to 2). With the text corpus prepared, we will apply NLP to organize common language and themes and conduct a social network analysis using bibliometric and scientometric methods to visualize citation networks that emerge from the selected texts. We will develop the NLP methodology iteratively to adapt it for the task at hand and decide on the model that offers the top performance (the “champion” model) based on various evaluation indices. We will also leverage NLP to visualize relevant information and findings that will inform and facilitate the synthesis of the material.

Textbox 1. Step-by-step description of natural language processing.

1. Extraction and organization of included articles (ie, corpus development)
2. Text preprocessing, including tokenization, stop word removal, and image removal
3. Data transformation and vectorization
4. Loading of the data to make it available for reusability and machine learning experimentation
5. Clustering (k-means) and evaluation
6. Latent Dirichlet allocation modeling and evaluation
7. Latent Dirichlet allocation model visualization
8. Information extraction
    - Entity recognition
    - Identification of top frequent terms
9. Network analysis
    - Data structures, bibliographic metadata management, and data transformation
    - Network visualization of citations, coauthorships, and term co-occurrences
    - Node top “cardinalities” and “centralities” measurement

Clustering, Topic Modeling, and Information Extraction

To analyze content from the identified texts, we will use NLP techniques such as clustering, topic modeling, and information extraction (ie, the extraction of elements such as frequent terms or collocations) to conduct a more granular analysis of concepts and organize a knowledge graph in more detail [37].

Probabilistic models in machine learning help segment data based on their semantic similarities. Semantically effective representations such as bag-of-words and term-frequencies-inverse-document-frequencies will be used to transform text into vector space, allowing for traditional machine learning algorithms to process them (steps 3 to 4). We will use latent Dirichlet allocation (LDA) topic modeling for content analysis and clustering (steps 5 to 6) [37]. LDA is a

probabilistic clustering model that generates latent and important topics in the documents using semantic weights. We will extend the LDA to visualize the topic terms within each cluster (step 7) [38]. The objective of clustering the corpus is to group together semantically similar contexts in a basket and extract relevant and important terms that associate together to form the main topics latent in the text. For entity recognition, an activity that involves processing a text and identifying certain occurrences of important words or expressions as belonging to particular topics of interest, we will use SpaCY, an industrial-grade, off-the-shelf model with state-of-the-art evaluation techniques to identify the most frequent names in the text (step 8) [39].

In the absence of labeled data, evaluation of the clustering methods will be based on the semantic attributes of "similar" text, measured by indices such as coherence and mutual information [40]. Other clustering algorithms, such as k-means, can also be used to decide the optimal number of clusters and the champion model using evaluation metrics such as the coherence, silhouette (a cluster validity measure that optimizes the betweenness within the densest clusters so that the furthest clusters contain the closest points possible) and elbow methods. Using the coherence and elbow methods, we will evaluate the quality of our clustering algorithms [41]. We will also evaluate how different clustering methods correspond with the subtopics and the titles of the paper groups using the Cohen κ score. As an example, we may derive clusters that illustrate how digital tools in family medicine residency education are (1) influencing educational content, (2) affecting education governance, or (3) inducing innovations in family medicine education. These insights can then be overlaid with the time dimension to observe directions, gaps, and emerging interests.

Results from these analyses will be compared to findings from the manual thematic analysis to identify similarities and differences between the 2 approaches and may suggest strengths, limitations, and opportunities for applying NLP to the data synthesis phase of scoping reviews. For example, this process may help rectify some of the challenges associated with literature reviews, such as heterogeneity in classifying research themes and maintaining a reliable balance between coverage and focus [42].

Bibliometric and Scientometric Methods

Using social network analysis and relevant indices, such as cardinality and centrality of nodes, we will explore the evolution and emergence of research on digital learning tools by studying the patterns and connections between authors, fields, and journals during the review study period (step 9) [43].

We will perform a social network analysis of the included citations by extracting meta information from the digital library of included articles and construct bibliographic data in standard formats. This will allow for subsequent visualization of citation networks using open-source graph visualization tools [44]. Coauthorship networks can depict scholarly teamwork and the main players given different thresholds (ie, at least 2 articles), providing insights into research trends and activities and their structures [43,45,46]. Another insightful network will be keyword co-occurrence, in which the size of the nodes will indicate the frequencies of terms and subject headings in the literature corpus. Lastly, a citation network will be produced given a threshold of at least "k" citations (k will be decided as per the norm reference sizes in the literature).

Stage 6: Patient and Public Involvement

This scoping review was co-designed by a multidisciplinary team using an integrated knowledge translation approach. Stakeholders and knowledge users, including clinicians, medical educators, digital learning tool developers, researchers, and students, will contribute to all stages of the study. Team members assisted in developing the research question, defining the scope of the search strategy, and identifying relevant data extraction elements. They also assisted in developing a methodology for the gray literature advanced site search by identifying websites and organizations that may contain relevant information. Some stakeholder group members will participate in screening and data extraction, and all group members will be invited to contribute to the data analysis, interpretation of the results, and preparation of findings for dissemination.

Results

As of October 2021, we have completed stages 1, 2, and 3 of the scoping review. We identified 132 studies for inclusion through the academic literature search and 127 relevant studies in the gray literature search (Figure 1). Further refinement of the eligibility criteria and data extraction has been ongoing since September 2021 (stage 4). Collation of the results (stage 5) and preparation for dissemination (stage 6) are expected to occur between September 2021 and March 2022.

Discussion

Overview

In this scoping review, we will identify and consolidate information and evidence related to the use of existing digital learning tools in postgraduate family medicine training. Based on the preliminary results of this review, we hypothesize that our findings will demonstrate heterogeneity in the types and diversity of tools being used. Additionally, this scoping review will lay a foundation for exploring the effective evaluation of tools as part of future research.

The Use of NLP in Scoping Review Methodology

Although our protocol is based on established methodology [21-23], our application of NLP techniques is novel. These NLP techniques may uncover influential authors or publications and popular themes in publishing practices, which will provide important information for future literature reviews and serve as helpful context for interested newcomers in this field of research.

The breadth of literature regarding the use of digital learning tools is vast. Previous systematic reviews have identified high levels of heterogeneity in the types of digital learning tools used, measures of effectiveness, and main findings [8,10-14,18]. As such, NLP techniques may allow us to begin understanding patterns in the emergence of this topic in the literature and structuring or classifying the diverse types of digital learning tools that have been described, among other insights. Using

NLP techniques such as clustering, topic modeling, and information extraction will allow us to organize common themes, content areas, and concepts between texts. This may provide a more robust thematic analysis and represents an opportunity to compare findings from traditional human-developed analysis with those identified by computational and NLP techniques [26]. Using computational techniques will provide the opportunity to explore how these techniques may be leveraged in the methodology of scoping reviews [26].

Furthermore, the application of NLP may be particularly well suited for the present review of digital learning tools in medical education, given that it is an emerging area of research with key terms that are not yet supported by well-indexed, comprehensive bibliographic databases [47]. The use of supplemental computational techniques, such as calculating cardinality and centrality of the articles based on a network model of references, will help us identify and measure the important position of the concepts within the body of knowledge. It will support traditional researcher-driven review strategies and be helpful for describing and understanding this vast and growing body of literature on digital learning tools.

Additionally, social network analysis to examine coauthorship networks has been previously applied in medical, health care, and medical education research with the aim of promoting or strengthening research collaboration [46,48-50]. Therefore, generating an understanding of the nature of collaboration in digital learning for the medical education research community may accelerate cooperative research initiatives by connecting leaders and innovators across various disciplines. Given that the development of digital learning tools is inherently an interdisciplinary pursuit, such coauthorship network analysis will be an important step in driving innovation in this field. Finally, the methods we propose to describe and group research studies are novel, and to our knowledge, have not been explored in medical education research. The utility of automating the data extraction and descriptive phases of scoping reviews through NLP depends on the nature of the dataset (ie, the selected articles) and the information sought (ie, the review question). Thus, this study represents an opportunity to establish the feasibility of these techniques in this context and produce significant foundational knowledge to support the utilization of these powerful techniques in literature reviews in the rapidly growing area of medical education research and its related disciplines.

Limitations

Development of this protocol for our review serves to provide a detailed structure for the scoping review and to improve the transparency of the research. However, our study has several limitations. Since the objective of the review is to identify digital learning tools currently being used, we will not provide an evaluation of the quality of the digital learning tools. Additionally, digital learning tools that are not described in the academic and gray literature will not be captured in this scoping review. Any deviation from the scoping review protocol described here will be outlined in the final manuscript, accompanied by a rationale for the change.

Dissemination Plan

The findings from this scoping review will be presented to an interdisciplinary team at the University of Ottawa's Department of Family Medicine in order to inform the department on the current landscape of digital learning tools and aid the development of new and effective digital tools, with the aim of eventually designing digital tools for the department. As an institution that prioritizes innovation, the Department of Family Medicine actively collaborates with engineering departments and engages in co-design to develop adaptive and intelligent digital tools for education. The completion of this study, with its novel scoping review protocol, will involve continuous collaboration and effective knowledge translation among an interdisciplinary group of researchers. This interdisciplinary environment is key to enabling the exploration of novel applications of NLP in medical education and research, and it will foster further collaboration to drive innovation at the intersection of medicine and artificial intelligence. We plan to share consolidated findings in an article that will be submitted for publication in a peer-reviewed journal. Finally, findings will be disseminated through academic platforms, such as conference presentations and meetings, which will not only inform the collaborative development of digital tools to be integrated into medical curricula, but also provide an exciting, innovative, and novel framework for the application of NLP methods in medical education research. We hope that this information is of great value to educators and trainees interested in using existing tools, innovators looking to design digital learning tools that meet current needs, and researchers involved in the study of digital tools.

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Authors' Contributions

CS, AR, MH, SK, HY, TM, RH and CL designed the study. All authors reviewed the project protocol and provided important feedback to ensure the research would be relevant for the research end users. CS, HY, RH, TM and SK have started data collection. CS, HY, AR, and RH drafted and revised the manuscript. All authors provided feedback and critical revisions for important intellectual content. All authors approved the final draft of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Academic literature search terms.
[DOCX File , 29 KB - resprot_v11i5e34575_app1.docx]

Multimedia Appendix 2
Search Strategy for Academic Databases.
[DOCX File , 14 KB - resprot_v11i5e34575_app2.docx]

Multimedia Appendix 3
Search strategy for Google search engine.
[DOCX File , 12 KB - resprot_v11i5e34575_app3.docx]

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Abbreviations

LDA: latent Dirichlet allocation
NLP: natural language processing
RCT: randomized controlled trial

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Protocol

Humanizing Health and Social Care Support for People With Intellectual and Developmental Disabilities: Protocol for a Scoping Review

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Abstract

Background: Health care is shifting toward a more person-centered model; however, people with intellectual and developmental disabilities can still experience difficulties in accessing equitable health care. Given these difficulties, it is important to consider how humanizing principles, such as empathy and respect, can be best incorporated into health and social care practices for people with intellectual and developmental disabilities to ensure that they are receiving equitable treatment and support.

Objective: The purpose of our scoping review is to provide an overview of the current research landscape and knowledge gaps regarding the development and implementation of interventions based on humanizing principles that aim to improve health and social care practices for people with intellectual and developmental disabilities.

Methods: The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) and PICOS (Population, Intervention, Comparator, Outcome, and Study) frameworks will be used to structure the review. A total of 6 databases (PubMed, MEDLINE, Embase, CINAHL, PsycINFO, and Web of Science) will be searched for English articles published in the previous 10 years that describe or evaluate health and social care practice interventions underpinned by the humanizing principles of empathy, compassion, dignity, and respect. Two reviewers will screen and select references based on the eligibility criteria and extract the data into a predetermined form. A descriptive analysis will be conducted to summarize the results and provide an overview of interventions in the following three main care areas: health care, social care, and informal social support.

Results: The results will be included in the scoping review, which is expected to begin in October 2022 and be completed and submitted for publication by January 2023.

Conclusions: Our scoping review will summarize the state of the field of interventions that are using humanizing principles to improve health and social care for adults with intellectual and developmental disabilities.

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KEYWORDS

developmental disabilities; intellectual disability; delivery of health care; patient care management; social work; social support; patient-centered care; empathy; respect; social care

Introduction

Background

Although recent efforts are being made to address health inequities, people with intellectual and developmental disabilities (IDDs) can experience difficulties in accessing high-quality care [1,2]. People with IDDs are more likely to experience earlier health limitations and have social determinants that are associated with poor health. Health care professionals (for this paper, defined as any trained individual providing some type of health or social care support to people with IDDs; eg, clinicians, health care support workers, allied health professionals, social care workers, etc) are not necessarily trained and equipped to address the needs of people with IDDs in an equitable and empowering way [1,3]. The delivery of health care has recently shifted toward a more person-centered, humanizing model [4]. Person-centered or patient-centered models of care empower patients to share responsibility for their health, enhance the personalization of care, and enable patients to make informed choices about how to manage their health needs [5]. This shift demonstrates a recognition of the importance of underpinning care practices with humanizing principles, such as empathy and respect for people's dignity, agency, uniqueness, sense of place, personal journey, and holistic well-being [6,7].

Delivering this model of care to a high quality presents a potential challenge in people with IDDs, as they can experience barriers to equitable health care access, such as difficulty with communication and a lack of engagement. Feelings of fear or can also be exacerbated by a lack of health education, a lack of training for health care professionals, the negative attitudes of health care professionals, short consultation times, and multimorbidities (which can also increase the complexity of the care needs of people with IDDs) [8-11]. Clinically, people with IDDs have a significantly shorter life expectancy than that of the general population [12]. This is influenced by potentially preventable causes that are impacted by inequalities in the access to and provision of care, which are disproportionate to those in the general population [13]. Given the health inequities faced by people with IDDs, there is a clear need for improved means of ensuring that people with IDDs are treated with empathy, dignity, and other humanizing principles during their interactions with health and social care services.

Rationale

Although several reviews have been conducted that focus on access to and experiences with health care among people with IDDs [14-17], none of these reviews included an overview of interventions that provide humanizing care for people with IDDs. Searching PROSPERO with the string *intellectual disabilit* OR developmental disabilit* AND healthcare OR health care OR social care AND humanising OR person centred OR patient centred OR empathy OR dignity OR respect* did not identify any reviews on this topic. Therefore, there is a need to conduct a comprehensive summary of what interventions are being developed and delivered to improve care for people with IDDs in accordance with humanizing principles.

Previous reviews have examined the experiences of, challenges to, and barriers for people with IDDs in accessing health care services [14-18]. The key barriers identified included difficulties with communication between patients and health care professionals; poor-quality services and a lack of services, which are often due to deficits in health care professionals' understanding, training, and skills; and other organizational barriers related to procedures or facilities [14-18]. Although the databases and years searched were comprehensive, the reviews focused on particular services (mental health services [17], physical health care services [18], or services in acute care settings [14,15]) or populations (people with autism [18]). One review was published in 2005 and therefore does not reflect any recent changes in health care delivery [16]. Although the reviews examined the experiences of people with IDDs, they did not provide an overview of any efforts that were being made to address and mitigate the barriers identified, and they did not specifically address humanizing principles. A review by Busch et al [6] in 2019 focused on the humanization of care; it highlighted the importance of empathy and respect in patient-provider interactions and the availability of sufficient time and resources for supporting this, but it was not specific to people with IDDs. None of the reviews identified focused on informal social support for adults with IDDs. The search of PROSPERO only identified 2 planned or ongoing reviews that were relevant (a review of the accessibility of public health services for people with IDDs and a review about improving social care outcomes). However, neither review focused on humanizing principles or provided a broad overview of interventions, and one was removed for no longer being within the scope of PROSPERO.

Given the barriers and health inequities that people with IDDs experience when accessing health and social care services, an overview of the potential solutions being explored, developed, and implemented is needed. A scoping review will provide a summary of the state of the field, the inclusion of humanizing principles in interventions for people with IDDs, and the strengths and weaknesses of these interventions. This will help to inform directions for future research and development and provide an initial assessment of the potential of these interventions.

Aim and Research Question

The aim of our review is to identify and provide an overview of interventions that promote health and social care practices for people with IDDs that are based on humanizing principles. To do this, the scoping review will focus on the following

research question: *What professional interventions are being developed and delivered to promote empathy, dignity, kindness, and recognition in health and social care encounters involving people with IDDs?*

Methods

Overview of the Study Design

The review and search strategy were structured using the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews; Multimedia Appendix 1) [19] and PICOS (Population, Intervention, Comparator, Outcome, and Study) frameworks (Textbox 1).

Textbox 1. PICOS (Population, Intervention, Comparator, Outcome, and Study) framework.

Population

- Adults (aged >18 years) with intellectual and developmental disabilities

Intervention

- Formal and informal health and social care interventions and practices underpinned by the humanizing principles of empathy, compassion, dignity, kindness, and recognition (eg, referrals, assessments, clinical judgments, treatments, service management and commissioning, multiagency team working, clinical and social training, informal communities, and peer support systems)

Comparator

- How defined interventional types compare to the general adult population (outside of the review population's scope); however, no comparator is required for inclusion

Outcome

- The primary outcome will be the inclusion of humanizing principles in professional interventions for health and social care encounters involving people with intellectual and developmental disabilities
- Secondary outcomes will include the types and characteristics of the interventions, study types, perspectives of people with intellectual and developmental disabilities about the interventions, and strengths and limitations of the interventions

Study types

- All study types that describe or evaluate a relevant intervention will be eligible for inclusion
- Reviews, meta-analyses, and conference abstracts or posters in which no full text is available will be excluded

Search Strategy

Our review will search the following six databases to identify potentially relevant references: PubMed, MEDLINE, Embase, CINAHL, PsycINFO, and Web of Science. Relevant Medical Subject Headings (MeSH) terms and keywords were identified for the search based on a preliminary examination of the literature and previous reviews conducted on related topics. These terms were grouped into 3 themes and were searched by using the following search string structure: *IDD (MeSH OR keywords) AND health and social care services (MeSH OR keywords) AND humanising principles (MeSH OR keywords)* (Table 1).

Table 1. Search strings.

Category	Medical Subject Headings	Keywords (in titles or abstracts)
Intellectual and developmental disabilities	*Developmental Disabilities OR Intellectual Disability OR Learning Disabilities OR Autistic Disorder*	*"Developmental disabilit*" OR "learning disabilit*" OR "intellectual disabilit*" OR "learning disorder*" OR "developmental disorder*" OR "special need*" OR "mental retardation" OR "mental inadequac*" OR "mental handicap" OR autis* OR "Down syndrome" OR "Down's syndrome" OR "fetal alcohol" OR "learning difficult*" OR "congenital cognitive impairment" OR "mental impairment*" OR "pervasive development" OR "ADHD" OR neurodivers* OR "neurodevelopmental disorder*"*
Health and social care services	*Delivery of Health Care OR Community Health Services OR Social Work OR Social Support OR Patient Care Management OR Patient Care Team OR Quality of Health Care OR Caregivers*	*Healthcare OR "health care" OR "health and social care" OR "primary care" OR "secondary care" OR "specialist care" OR "palliative care" OR "end of life care" OR "care service*" OR "healthcare service*" OR "health care commissioning" OR "health commissioning" OR referral* OR assessment* OR diagnos* OR "clinical judgement*" OR "clinical judgment*" OR formulation OR investigation* OR treatment* OR "service management" OR "multi-agency team" OR "multi-disciplinary team*" OR "clinical training" OR "social training" OR "professional development" OR "social care" OR "social work" OR "social service*" OR "care support" OR caregiver* OR "social care commissioning" OR "social support" OR "peer support" OR "informal care" OR "information social care" OR "unpaid care" OR carer* OR "informal carer*" OR "informal social support" OR "community care" OR "care networks"*
Humanizing principles	*Patient-Centered Care OR Empathy OR Respect*	*Empathy OR compassion OR dignity OR kindness OR recognition OR respect OR humanis* OR humaniz* OR humanity OR "patient-centred care" OR "patient-centered care" OR "person-focused care" OR holistic OR relationship OR equity OR equality OR fair*

Inclusion Criteria

The review will include studies that describe or evaluate any type of health and social care intervention for people with IDDs (eg, training, digital support, and organizational or physical changes) that are based on humanizing principles, including empathy, dignity, and respect. Studies will be included if they describe the development of such an intervention or evaluate the implementation of such an intervention (at any stage). Therefore, all study types that describe or evaluate an intervention will be eligible for inclusion. Studies concerning people with any type of IDD will be eligible for inclusion.

Exclusion Criteria

As the aim is to provide a broad overview of interventions and humanizing health care practices for people with IDDs, there are few exclusion criteria. The focus of the review will be on adults, so studies concerning humanizing health care interventions for children and adolescents with IDDs (aged under 18 years) will be excluded. Likewise, studies that explore humanizing health care interventions for the general population, with no specific reference to people with IDDS, will also be excluded. Studies that do not describe the development or evaluation of a specific humanizing intervention (or a set of interventions) for adults with IDDs will be excluded (eg, reviews, meta-analyses, and conference abstracts or posters with no full-text versions). To ensure that the review examines recent interventions and practices, the search will be limited to the previous 10 years; articles published before 2011 will be excluded. Studies published in languages other than English will be excluded, as the review team has limited ability to effectively undertake the analysis of such studies.

Screening and Article Selection

References will be stored and any duplicates will be automatically removed using the citation management software EndNote X9 (Clarivate). The first screening will be performed by inputting keywords related to the inclusion and exclusion criteria into EndNote X9's search function. Two independent reviewers will screen the remaining titles and abstracts and then the full texts. The reasons for exclusion at the full-text screening stage will be recorded. Any disagreements on eligibility at either stage will be discussed by the two reviewers, and a third reviewer will be consulted if agreement cannot be reached. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram will be used to record the details of the screening and selection process (and reasons for exclusion) to ensure reproducibility and transparency.

Data Extraction

The two reviewers will extract predetermined outcomes from the full texts (Textbox 2). As in the article selection process, any disagreements between the reviewers will be discussed, and they will be resolved by a third reviewer if necessary.

Textbox 2. Article information and data to be extracted.

General study information

- Year of publication
- Sample size (if applicable)
- Study type
- Target population (eg, people with a specific developmental disability)

Health and social care practices and interventions

- Category of intervention (health care, formal social care, or informal social care)
- Type of intervention
- Aim of intervention
- Humanizing principle(s) that the practice or intervention is based on
- Brief description of intervention (features and components)

Evaluation of intervention

- Strengths of the intervention
- Limitations of and barriers to the intervention
- Perspectives of people with intellectual and developmental disabilities (if reported)

Data Analysis and Synthesis

A large variety of study types, measures, and outcomes is expected. As such, a descriptive analysis will be used to provide an overview of the different types of health and social care interventions via a 3-pronged approach. The interventions will be categorized based on their main area of focus as follows: health care, formal social care, or informal social care. On the basis of these categories, a thematic analysis of the evaluations of the interventions will be conducted to summarize the common strengths and weaknesses of, and perceptions toward, the interventions. Common themes will also be explored across the three categories to determine similarities, differences, and gaps in the inclusion of humanizing principles in interventions across different care contexts. Any qualitative data related to the perspectives of people with IDDs that are included in the studies reviewed will also be summarized by using a thematic analysis.

Results

The full scoping review has not yet begun. It will be started in October 2022, and it is expected to be completed and submitted for publication by January 2023.

Discussion

Comparison to Prior Work

Recent reviews related to the access of health care services by people with IDDs identified a variety of barriers [15,17,18], but no reviews were identified that examined efforts to address these barriers by using humanizing principles. Our scoping review will add to the field by providing a summary of the current state of the field of research regarding the interventions that aid the humanizing of health and social care for adults with IDDs.

Limitations

One limitation of the scoping review is that a risk of bias assessment will not be performed on the studies. Risk of bias assessments are not a standard requirement for scoping reviews [19]; however, the lack of a risk of bias assessment limits the ability to examine research gaps related to research quality, which could provide further insight on areas for improvement in the design, development, and evaluation of humanizing interventions for health and social care for people with IDDs. Another limitation is that the scoping review methodology does not include searching for grey literature. Grey literature will be excluded to keep the broad scope of the review manageable and to focus on evaluations that have been peer reviewed, since an independent quality assessment will not be conducted. However, this means that the review has the potential to overlook some promising interventions that have been developed but not formally described or evaluated.

Conclusions

By providing a clear overview of what is currently being explored, the strengths and weaknesses of interventions, and the gaps in the field, our scoping review will help to inform the design and development of interventions and health and social care practices that are based on humanizing principles to ensure that people with IDDs are treated with dignity, empathy, and respect. The health inequities that people with IDDs face, their higher likelihood of needing care, and the shift toward more person-centered health care make this issue particularly important to address. A clear understanding of what efforts are being made in this area will help to identify good practices and areas for improvement that will enable future interventions to facilitate more humanizing care and treatment. Using established and developing networks and publishing reviews to broadcast current findings and enhance our understanding of the current state of the field are just 2 of the many possible avenues for

influencing health practitioners' practices. Once current strategies and interventions have been identified and examined, future work will have a solid base upon which to design improved interventions and implement the learnings from the review into clinical and social care practices. Conclusions that reflect the data, acknowledge the limitations of the scoping review, and indicate key areas for future research will be drawn and disseminated via journal publication. The findings will also be summarized in plain English for their distribution to any relevant clinical or governmental stakeholders that are identified during the review.

Acknowledgments

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Authors' Contributions

RS and DG conceived the concept for the protocol and developed the research question and PICOS (Population, Intervention, Comparator, Outcome, and Study) framework. MMI drafted the protocol, which was reviewed by KL, RS, DG, RL, and EM. TH and MMI revised this paper in response to peer reviews and editorial feedback.

Conflicts of Interest

EM is the editor in chief of *JMIRx Med*. All other authors declare no conflicts of interest.

Multimedia Appendix 1
PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist.
[DOCX File , 84 KB - resprot_v11i5e31720_app1.docx]

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Abbreviations

IDD: intellectual and developmental disability
MeSH: Medical Subject Headings
PICOS: Population, Intervention, Comparator, Outcome, and Study
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

The Impact of Health Care Funding on Interprofessional Collaboration and Integrated Service Delivery in Primary and Allied Care: Protocol for a Scoping Review

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Abstract

Background: Improving funding models and implementing policies that facilitate greater interprofessional collaboration and integration at the primary and allied health level could improve the ongoing quality and safety and future sustainability of the wider health care system by reducing inefficiencies and inequalities. Defining these key health care funding–related models, policies, and concepts, identifying research gaps, and systematically mapping the associated literature will inform future research on this topic.

Objective: The aim of this scoping review is to provide a descriptive overview of contemporary health care funding models and the key policies involved in the delivery of primary and allied health care. Further, it will investigate the impact these models and policies have on interprofessional collaboration and integrated service delivery at the primary and allied health care levels.

Methods: A search of published and grey literature will be conducted using the following databases: the Allied and Complementary Medicine Database, CINAHL, Embase, Emcare, MEDLINE, PsycINFO, Scopus, Open Access Theses and Dissertations, and Web of Science. The search will be limited to resources available in the English language and published since 2011. Following the search, an independent screening of titles and abstracts will be undertaken by 2 independent reviewers, with a third reviewer available to resolve any potential disagreements. Full-text resources will then be assessed against the inclusion criteria following the same process. Extracted data will be presented using a convergent narrative approach, accompanied by tables and figures.

Results: Electronic database searches have retrieved 8013 articles. The results of this scoping review are expected in May 2022.

Conclusions: The findings from this review will be used to inform future research projects investigating the role of primary health care funding, interprofessional collaboration, and service integration in improving health care access, efficiency, effectiveness, and sustainability.

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KEYWORDS

allied health; healthcare funding; interprofessional collaboration; integrated healthcare; primary health; primary care

Introduction

Background

According to the World Health Organization (WHO), to meet current and predicted future global health care needs, governments and health care funding bodies worldwide must prioritize health care funding models and policies that embrace universal health coverage (UHC) [1-4]. Health systems designed and funded to reflect the principles of UHC ensure that everyone who needs access to health care resources can access the services they need at a time and place that is suitable and without experiencing financial hardship [1-4]. In general, health systems considered to be funded effectively do not necessarily spend the most money or account for the highest percentage of gross domestic product per capita [5,6]. Rather, more efficient, and strategic health care spending is directed toward systems favoring funding models and policies that value team care approaches and health care professionals moving away from traditionally fragmented professional practice silos where disciplines are largely segregated [7-12]. In this context, instead of health care professionals working as specialists in relative isolation, providers from different professional backgrounds are encouraged to work together through interprofessional collaboration [7-12].

Interprofessional collaboration, by definition, uses the collective knowledge and expertise of 2 or more health care professions working together to offer more appropriate, timely, comprehensive, and person-centered health care to consumers [2,6,8-12]. In health care systems with effective funding models and policies, interprofessional collaborations are integrated horizontally across different health care professions and vertically between each level of the health care system [8,9]. This integration is inclusive of tertiary (eg, hospitals), secondary (eg, specialist health services such as psychiatry, oncology, and surgery), and primary (eg, general and community health services, such as general practice, community health, and allied health), levels of care [8,9]. As such, service integration connects the different levels and disciplines involved in the health care system with administrative and organizational support [8,9]. In turn, this can improve clinical outcomes, increase consumer and clinician satisfaction with service provision, and promote more efficient use of health care resources, staff, and funding [8,9].

Since 1978's Declaration of Alma-Ata, which was more recently renewed and ratified with 2018's Declaration of Astana, the WHO has strongly endorsed commitments to increase health care funding and improve funding models and policies at the primary level [1,8,9,13-15]. A growing body of evidence suggests that concentrating on primary health and structuring future health systems around strong primary foundations will have the greatest impact on efforts to move toward UHC [1,8,9,13-15]. Focusing on funding improvements at this level is understood to have the most significant impact as the primary level is the largest, most professionally diverse, and most geographically spread level of care and is responsive to the determinants of both health and ill-health [1,2]. These features also suggest that primary health is the most naturally accommodating and well-suited to interprofessional collaboration and integrated service provision [8,9,16,17]. Likewise, they contribute to primary health by being uniquely positioned to assist the largest numbers of people and to do so earlier during illness or injury progression [1,2,6]. As such, a strong primary health care system can delay, mitigate, and in some cases even prevent the need to escalate service provision to more specialized, centrally located, scarce, and more costly secondary and tertiary health care services [1,2,6,8].

However, despite many varied and concerted international efforts to commit to UHC goals and improve primary health care funding models and policies [2,4,6], primary health clinicians around the world are still working in underfunded vertically and horizontally isolated professional practice silos [7-12]. Funding policies and models are also ambiguous, creating many barriers to interprofessional collaboration and integrated health care delivery [2,6,15,18,19].

Since the beginning of the COVID-19 pandemic, existing health care inequities embedded within contemporary funding models and policies have become increasingly apparent [3]. In some cases, the divide between already marginalized groups has significantly worsened, putting extra pressures on health care systems to limit who, how, where, and when consumers can access health care services as well as the financial cost for doing so [3]. This increasing divide in health care equity is also occurring in the context of depleted financial reserves, stretched and interrupted global resource and supply chains, and current and predicted future health care staffing shortages [3].

Although these issues present substantial challenges to global economic and health systems, they also offer governments a unique window of opportunity to rethink health care funding models and policies. By reorienting health systems to better reflect the fundamental values of UHC as part of the pandemic recovery process, there is potential to instill greater ongoing financial and workforce sustainability [3]. However, to maximize improvements to health care efficiency and access, more research is needed to determine if and how health care funding policies and models might impact interprofessional collaboration and service integration, starting at the primary health care level.

A preliminary search of MEDLINE, CINAHL, Open Science Framework, and JMIR Research Protocols identified no current or in-progress reviews focusing on the role of health care funding in relation to interprofessional collaboration or integrated health care. Instead, previous works have considered the impact of reimbursement systems on equity in access to primary care, the quality of primary care [20], and interprofessional collaboration and integrated service delivery in primary and allied health care [12,14,21]. Therefore, by investigating the impact that funding models and policies may have on interprofessional collaboration and integrated health care service delivery at the primary care level, the knowledge gained by this scoping review is intended to address a notable research gap. Further, it will inform future research projects investigating the role of health care funding, interprofessional collaboration, and service integration in improving health care

access, efficiency, effectiveness, and sustainability in line with UHC ideals.

Review Questions

Primary Research Question

How do health care funding policies and models impact interprofessional collaboration and integrated service delivery in primary and allied care?

Secondary Research Questions

The secondary research questions are as follows:

1. Which key health care funding models and policies determine health care funding in primary and allied health care?
2. Which key characteristics of interprofessional collaboration and integrated health care have been researched in relation to health care funding in primary and allied care?
3. What impact does funding have on professional roles and responsibilities when working in an integrated primary or allied health care role?

Methods

Overview

The proposed scoping review will be conducted in accordance with the JBI Institute methodology for scoping reviews [22-24] and will use the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for Scoping Reviews) reporting guidelines and checklist to ensure appropriate methodological rigor and transparency [23].

Inclusion Criteria

Participants

This review will consider literature pertaining to adults (defined as individuals ages 18 years and older) who are employed within the specified primary and allied health care disciplines or are the recipients of care provided by these disciplines.

For the purposes of this review, primary health care professions will include physicians, physician assistants, nurses, and allied health professionals identified as working in primary health care settings. There is no international consensus on what constitutes allied health or the specific professions and disciplines included within the allied health field [25]. Therefore, the extensive list of potential inclusions makes achieving sufficient data saturation for all nationally and internationally recognized allied health professions impractical within the constraints of this review. As such, allied health professions were selected for inclusion based on the following criteria: (1) being recognized as an allied health profession and represented by a professional association member or affiliate member of Allied Health Professions Australia [26], (2) having a scope of practice that includes interprofessional collaboration and integration at the primary health care level, (3) having a practice that is treatment-based rather than diagnostic, and (4) not being recognized as an alternative health or complementary therapy discipline.

Therefore, the allied health professionals selected for inclusion in this scoping review are audiologists, chiropractors, dietitians, exercise physiologists, hand therapists, myotherapists, occupational therapists, optometrists, orthoptists, orthotists, osteopaths, physiotherapists, podiatrists, prosthetists, psychologists, rehabilitation counselors, social workers, and speech and language therapists. Multimedia Appendix 1 further outlines the rationale for the exclusion of several other allied health professions. Due to feasibility constraints, a decision was made to exclude literature concerning interprofessional collaboration and service integration involving secondary (eg, specialist services such as psychiatry, oncology, or surgery) or tertiary (eg, hospital) levels of care.

Concept

The following 3 concepts will be explored in this scoping review: health care funding, interprofessional collaboration, and integrated service delivery. Regarding health care funding, factors of particular interest will include health care funding models (eg, compensable, noncompensable, public, and private funding models) and health care funding policies (eg, governmental, nongovernmental, health system, organizational, or professional funding policies). Health care funding characteristics are also of interest. These will include units of funding (eg, per service, per hour, per case, or per capita funding), funding principles (eg, input-based, output-based, performance-based, or achievement-based funding), the timing of funding (eg, prospective, or retrospective funding), and funding modes (eg, cash, recourses, assets, or in-kind services) [27].

The elements of interprofessional collaboration addressed by this review will focus on the relationships, interactions, and collaborative processes between primary and allied health clinicians (eg, writing and receiving referrals and participating in case conferences, clinical discussions, and multipractitioner appointments, assessments, and interventions) [7,9-12,18]. As for health care integration, the type (eg, normative or functional integration), and level (eg, system, organizational, professional, or clinical integration), of horizontal connections between primary and allied health clinicians will be considered [3,6,8,9].

Context

This scoping review will consider health care funding policies and funding models operating at the primary health care level only. The primary level was selected as it has long been stipulated that improving health care funding and implementing policies that facilitate greater interprofessional collaboration and service integration between primary and allied health care at this level could improve the ongoing quality and safety and future sustainability of the wider health care system [2,3,8,14-17].

Types of Sources Included in the Search

All classifications of primary studies inclusive of quantitative, qualitative, and mixed-methods designs will be considered for inclusion. In addition, grey literature (including policy documents, government and organizational reports, academic theses and dissertations, white papers, book chapters, conference abstracts and proceedings, policy and procedure documents,

and opinion papers) will also be considered. Due to feasibility constraints, the scoping review inclusion criteria will be limited to digitally available contemporary literature accessible in the English language (due to the absence of dedicated funding that would typically cover the cost of translation services). A contemporary period of 10 years (from 2011 to 2021) was selected for this review to capture the increased interest in health care funding models and policies post economic recovery from the global financial crisis between 2007 and 2009 [28].

Search Strategy

The search strategy will aim to locate published and unpublished literature. An initial limited search of MEDLINE and CINAHL identified relevant articles and the index terms were used to develop a search strategy for MEDLINE (Ovid), with input from a professional research librarian (Multimedia Appendix 2). The search strategy, including all identified keywords and index terms, will be adapted as appropriate for each database and information source. Reference lists of retrieved literature that meet the inclusion criteria will be manually screened to identify additional relevant sources.

A search of published literature will be conducted using the following electronic databases: Ovid (Allied and Complementary Medicine Database, EMBASE, Emcare, MEDLINE, and PsycINFO), EBSCOhost (CINAHL), Scopus, and Web of Science. Sources of unpublished studies and grey literature to be searched will include GreyLit, Google Scholar, Open Access Theses and Dissertations, ProQuest Dissertations & Theses Global, Public Affairs Information Service Index, the WHO, and government health departments of primarily English-speaking countries (eg, Australia, Canada, New Zealand, the Republic of Ireland, South Africa, the United Kingdom, and the United States of America).

Source of Evidence Selection

Following search strategy implementation, the literature will be collated and uploaded into EndNote version X9 (Clarivate Analytics) for the removal of duplicate entries. Citations will then be exported to Covidence (Veritas Health Innovation), for screening of the titles and abstracts. Screening will be conducted against the inclusion criteria by 2 independent reviewers, with a third independent reviewer available to resolve any potential disagreements. Literature that the reviewers agree has met the inclusion criteria in the initial round of screening will be retrieved in full text and assessed against the inclusion criteria by the same independent reviewers, noting the reasons for any exclusions. The final search results (including reasons for exclusion) will be reported in full and presented using a PRISMA-ScR flow diagram [24].

Data Extraction

A total of 2 independent reviewers will use a custom data extraction tool developed by the authors to extract data from the included studies. Data for extraction (Textbox 1) will include descriptive information about the resource in terms of the author(s), year, country of origin, research aims, design, methodology, and methods. Information about funding model characteristics (including the funding type, level, unit, amount, principle, timing, and mode), funding policy characteristics (including the policy type, level, and scope), and practitioner characteristics (including the sample size and disciplines of health care practitioners), will be included. The research findings and any relevant outcome measures used in the research will also be extracted. This data extraction tool may undergo further modification and refinement during the data extraction process, with any changes to be clearly outlined in the final scoping review.

Although not a requirement of scoping review methodology [22,23], we decided to include an assessment of the level of evidence (using the Research Evidence Appraisal Tool and Non-Research Evidence Appraisal Tool) [29] and methodological quality (using the Crowe Critical Appraisal Tool [CCAT]) [30]. Including this optional step is intended to improve the robustness of the scoping review findings [31] and will allow for a more consistent analysis of what is predicted to be considerable heterogeneity in the literature.

Textbox 1. Sample data extraction elements.

Article information

- Author(s)
- Date
- Country of origin
- Aims or purpose
- Research methodology

Funding model characteristics

- Funding type, level, unit, principle, timing, and mode

Interprofessional collaboration and service integration characteristics

- Type and purpose of interprofessional collaboration and service integration

Practitioner characteristics

- Number and disciplines of primary and allied health care professionals

Findings

- Key findings related to how health care funding policies or characteristics impact interprofessional collaboration and service integration

Level of evidence and quality rating

- Level of evidence and quality rating will be performed using the Research Evidence Appraisal Tool and Non-Research Evidence Appraisal Tool [29].

Critical appraisal score

- Critical appraisal will be performed using the Crowe Critical Appraisal Tool Form (v1.4) [30].

Data Analysis and Presentation

Due to the broad nature of the research questions and the descriptive purpose of this scoping review, considerable heterogeneity of the literature is expected. It is anticipated that data presentation and analysis will need to accommodate for heterogeneity in the following factors:

- Research methodology and approaches (ie, qualitative, quantitative, mixed-methods, and nonexperimental literature will be considered, as will academic and grey literature)
- Funding model characteristics (ie, the funding model type, level, and scope)
- Funding policy characteristics (ie, the policy type, level, and scope)
- Interprofessional collaboration and service integration characteristics (ie, the type and purpose for collaboration and the type of service integration)
- Health care practitioner characteristics (ie, a range of primary and allied health care disciplines will be considered)

To meaningfully account for this complexity in the literature and provide a clear and accurate map of the evidence, a descriptive narrative analysis method of translating the research findings is proposed. Based on the 4-element convergent narrative synthesis framework outlined by Popay et al [31], a modified 3-element analysis encompassing (1) preliminary analysis, (2) robustness evaluation, and (3) relationship exploration is proposed.

The preliminary analysis will be conducted at the data extraction stage of the review. It will entail organizing and presenting the extracted data (Textbox 1) in tabular form to identify key themes. Also presented in the data extraction table will be the robustness evaluation. This will critically appraise the methodological quality of the literature using the CCAT (v1.4) [30] and assign a level of evidence to the included literature using the Johns Hopkins Nursing Evidence-Based Practice Evidence Level and Quality Guide Research Evidence Appraisal Tool [29] and Non-Research Evidence Appraisal Tool [29]. The relationship exploration will then consider the relationships and variability between the literature and identified themes, presented as a concept map that systematically highlights the evidence and research gaps that inform health care funding practices, policymaking, and research.

Results

Electronic database searches were conducted in November 2021, and 8013 results were retrieved. Title and abstract screening, full-text screening, data extraction, and manuscript completion are expected in May 2022. Upon completion of the final manuscript, the scoping review is intended for publication in a peer-reviewed academic journal.

Discussion

The findings from this review will identify the extent and nature of evidence regarding health care funding and how it impacts interprofessional collaboration and service integration at the primary and allied health care levels. These findings will be used to inform future research projects investigating the role of primary health care funding, interprofessional collaboration, and service integration in improving health care access, efficiency, effectiveness, and sustainability.

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Authors' Contributions

JA designed and wrote the scoping review protocol. LR and TB contributed to refining the protocol, search strategy, and data extraction methods. All authors have made substantive contributions to the development of this scoping review protocol and have approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Examples of excluded health professions.
[DOCX File , 13 KB - resprot_v11i5e36448_app1.docx]

Multimedia Appendix 2
Database search strategy.
[DOCX File , 47 KB - resprot_v11i5e36448_app2.docx]

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Abbreviations

CCAT: Crowe Critical Appraisal Tool
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
UHC: Universal Health Care
WHO: World Health Organization

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Protocol

Exploring the Equity Impact of Current Digital Health Design Practices: Protocol for a Scoping Review

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Abstract

Background: The field of digital health has grown rapidly in part due to digital health tools' potential to reduce health inequities. However, such potential has not always been realized. The design approaches used in digital health are one of the known aspects that have an impact on health equity.

Objective: The aim of our scoping review will be to understand how design approaches in digital health have an impact on health equity.

Methods: A scoping review of studies that describe how design practices for digital health have an impact on health equity will be carried out. The scoping review will follow the methodologies laid out by Arksey and O'Malley, the Joanna Briggs Institute, and the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist. The PubMed, Embase, Web of Science, and ACM Digital Library databases will be searched for peer-reviewed papers. The ProQuest Dissertations and Theses and Global Index Medicus databases will be searched for gray literature. The results will be screened against our inclusion and exclusion criteria. Subsequently, the data extracted from the included studies will be analyzed.

Results: As of March 2022, a preliminary search of the peer-reviewed databases has yielded over 4900 studies, and more are anticipated when gray literature databases are searched. We expect that after duplicates are removed and screening is completed, a much smaller number of studies will meet all of our inclusion criteria.

Conclusions: Although there has been much discussion about the importance of design for lowering barriers to digital health participation, the evidence base demonstrating its impacts on health equity is less obvious. We hope that our findings will contribute to a better understanding of the impact that design in digital health has on health equity and that these findings will translate into action that leads to stronger, more equitable health care systems.

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KEYWORDS

digital health; health equity; design; human-centered design

Introduction

Background

Health is an essential human right. However, for every human to have access to this right, it is necessary to reduce the health inequities that plague low-resource and high-resource countries alike [1]. Improving digital health and the design of digital health tools has long been heralded as one of the many ways to tackle such inequities in part because of the increasing pervasiveness of digital technologies and in part because from its inception, digital health has been put forward to strengthen health care systems and improve accessibility [2-6]. However, health equity, digital health, and design are broad, even fuzzy, concepts that need clear definitions in order to truly begin to analyze and understand the possible impact of the design of digital health on health equity.

Health equity definitions have changed throughout the years, depending on the context to which these definitions were being applied [7-9]. In the 1980s, the World Health Organization commissioned a series of papers through their "Equity in Health" program, and the foundational definition of inequity was formed: "The term 'inequity'...refers to differences in health which are not only unnecessary and avoidable but, in addition, are considered unfair and unjust" [10]. Throughout the 1990s and 2000s, different scholars and practitioners sought to refine this definition of *health equity* in order to identify measurable parameters and could therefore offer a higher degree of accountability and operationalization [7]. In 2018, Braveman et al's [11] definition was able to consolidate the work of decades prior. For them, "health equity means that everyone has a fair and just opportunity to be as healthy as possible. Achieving this...means reducing and ultimately eliminating disparities in health and in the determinants of health that adversely affect excluded or marginalized groups" [11]. According to this definition, health equity is both a process and an outcome, providing 2 different points for measurement. The process is reducing and removing the obstacles that prevent marginalized and excluded groups from achieving health, while the outcome is the absence of such obstacles. For our scoping review, when seeking to assess the health equity impact that design methods for digital health tools have, health equity will be evaluated either as a process or as an outcome. As a process, the health equity impact can be assessed by analyzing if and to what extent the development and implementation of digital tools, through design processes, ameliorate or eliminate health inequities. As an outcome, the health equity impact can be assessed by analyzing if and to what extent design processes for developing and implementing digital tools establish or enhance opportunities for increasing health and eventually achieving full health.

Although some consider the use of the telephone in the 1980s as one of the first forms of digital health [12], it was not until the 2000s that the technologies and tools that are today understood as digital health (then called *eHealth*) emerged. Just as with the concept of health equity, digital health definitions have changed throughout the years, and even now, there are multiple widely used and cited definitions of *digital health* in peer-reviewed, gray, and white literature (Textbox 1).

Textbox 1. The most widely cited and currently used definitions of digital health.

World Health Organization definition [13]

- "[T]he use of digital, mobile and wireless technologies to support the achievement of health objectives. Digital health describes the general use of information and communication technologies for health and is inclusive of both mHealth and eHealth."

Meskó et al [14] definition

- "[T]he cultural transformation of how disruptive technologies that provide digital and objective data accessible to both caregivers and patients leads to an equal level doctor-patient relationship with shared decision-making and the democratization of care."

Kostova [15] definition

- "Use of information and communications technologies to improve human health, healthcare services, and wellness for individuals and across populations."

Topol [16,17] definition

- "The convergence of smartphone-enabled mobile computational and connectivity capabilities is only one aspect of digital medicine; it also encompasses genomics, information systems, wireless sensors, cloud computing, and machine learning that can all be incorporated into new systems of health management, built around real-world, patient-generated data."

Food and Drug Administration definition [18]

- "The broad scope of digital health includes categories such as mobile health (mHealth), health information technology (IT), wearable devices, telehealth and telemedicine, and personalized medicine."

Healthcare Information and Management Systems Society definition [19]

- "Digital health connects and empowers people and populations to manage health and wellness, augmented by accessible and supportive provider teams working within flexible, integrated, interoperable and digitally-enabled care environments that strategically leverage digital tools, technologies and services to transform care delivery."

By reviewing the definitions above (Textbox 1), 3 main distinctives of digital health can be distilled. Digital health uses a vast array of digital technology; is used to improve health or prevent sickness; and is participatory in nature, meaning that patients and consumers are empowered to manage their health. For our scoping review, *digital health* will refer to any kind of tool that encompasses these three attributes.

A consensus exists—and is becoming stronger—that the role of digital health interventions is to increase existing access to health and strengthen health care systems [5,6,20]. It can be said that digital health interventions that widen the inequity gap, despite achieving positive results, fail as a whole because they neither increase the chances of individuals and communities to be healthy nor strengthen the health care system of which they are a part [20]. However, it would be simplistic to try to identify a single reason for why digital health interventions fail to reduce inequities. These interventions, which are complex in themselves, are deployed in complex environments (eg, multiple organizations, environments with competing priorities among stakeholders, etc) to address complex or "wicked" problems, such as reaching low-income populations to provide them with high-quality, affordable health care [3,21,22]. Not trying to understand the reasons behind why digital health interventions fail to reduce the inequity gap—or worse yet, why they widen it—would be unwise because this would perpetually hinder digital health from attaining its hallmark promise of reducing inequities across communities and among individuals through better and more accessible care [2-4]. For this reason, our research will focus on one of the characteristics of digital health technologies that is known to have a significant impact on equity—design [3].

Design, as a concept and as a field, has been gaining tremendous recognition in all spheres of life and work, touching "almost everything we experience today" and "[being] one of the most powerful forces in our lives, whether or not we are aware of it" [23]. Understanding how design affects processes, systems, objects, and people in the real world is the mission of countless businesses, nonprofits, and research organizations [24-26], yet in the incipient years of digital health, design was largely overlooked [27,28], resulting in significant resistance to use, the abandonment of technology, and detrimental health outcomes [29-31]. It has long been acknowledged that for digital tools and technologies to achieve their full potential, they need to be "people oriented," and this is achieved by designing them to have human requirements, instead of technological ones, at their center [32]. Across the board, the use of design approaches that take users and other stakeholders into consideration in order to develop more person-oriented tools has been gaining significant momentum [33]. Early on, this kind of design was mostly known as *user-centered design*. However, throughout the years, the term *human-centered design* has gained more prominence and has come to replace the term *user-centered design* [34].

Human-centered design can be considered an umbrella term [3], which at times has resulted in the term being used as nothing more than a catchword [35]. In order to include a wide breadth of literature regarding the use of human-centered design for digital health but to guard against uses of human-centered design that are too vague, our scoping review will use the practical set of components that human-centered design interventions should exhibit, which are described by Holeman and Kane [3] as follows:

- Participatory co-design: There should be evidence that the people who will use new tools or be impacted by them have been included in a meaningful and clear way. They are an integral part of the team.
- Supporting or augmenting human skills: There should be evidence that new tools will serve the people in a way that empowers them in their job or environment. The purpose of technology is not just to increase efficiency or oversight over a group of people.
- Attending to human values throughout the course of an iterative design and implementation process: There should be evidence of genuine interest for a whole person and for that person's circumstances. Purely technical issues do not drive implementation; instead, human values and technical requirements are considered in tandem and are refined and improved in a cyclical manner throughout the life of an implementation.

We believe that our research is relevant and necessary because it can contribute to the slowly growing body of evidence that shows how design practices in digital health have an impact on health equity by starting to bridge the gaps of knowledge between the assumed impact of digital health design on equity, the actual evidence of this impact in the literature, and the best design practices for helping to create more equitable health care systems.

Aim and Research Questions

The aim of this scoping review will be to understand how design approaches in digital health have an impact on health equity.

Because of the wide-reaching nature of design, understanding the impact that design is currently having on equity and how design methods can help eliminate inequities is crucial. To this end, our research will seek to answer the following research questions:

- Research question 1: Is there evidence in the existing literature that design methods for digital health have an impact on health equity?
  - How is the impact being measured?
  - What are the long- and short-term impacts?
- Research question 2: In the existing literature, can common approaches be identified regarding how design methods can help reduce health inequities?
  - If common approaches can be identified, can broad recommendations be made based on these approaches?

Methods

Scoping Review Method

Our research will follow the scoping review methodologies outlined by Arksey and O'Malley [36] and the Joanna Briggs Institute [37] to examine the current literature on how design practices are impacting equity in the field of digital health. The

PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist [38] will also be used to ensure that methodological standards are followed. This methodology was chosen over a systematic literature review for 3 reasons. First, scoping reviews better allow for exploring all relevant concepts in the broad and diverse research area of equity in the context of digital health design [39]. Second, unlike systematic literature reviews, which seek to present a synthesis of evidence, scoping reviews collect, organize, summarize, and present results—an approach that is better suited for working with data derived from different kinds of studies (eg, qualitative studies, quantitative studies, and mixed methods studies) [36]. Third, scoping reviews allow for inclusion and exclusion criteria to be crafted and refined iteratively as the topic becomes better understood by the authors and more evidence is uncovered [37].

Identifying Relevant Studies

The search strategy will be developed in a stepwise fashion, as seen in Textbox 2. This approach to developing a search strategy and searching the selected databases has been successfully used in other scoping reviews in the field of digital health [40-42].

Textbox 2. Steps for developing a search strategy.

Conducting searches in relevant databases

- By using already known keywords and studies, preliminary searches of relevant databases will help expand and refine search terms.

Searching key electronic, peer-reviewed databases and gray literature databases

- PubMed, Embase, Web of Science, and ACM Digital Library will be used to search for peer-reviewed papers.
- For gray literature, ProQuest Dissertations and Theses and Global Index Medicus will be searched.

Reviewing reference lists of relevant articles

- Reviewing reference lists can help identify studies that may have been missed in previous searches. It can be useful for uncovering new search terms.

Reaching out to experts through the Global Digital Health Network

- Reaching out to experts can be useful for further identifying previously missed studies. The Global Digital Health Network is one of the most relevant and active networks of professionals of digital health.

Keywords related to *design*, *equity*, and *digital health* will be used for the searches. To further identify relevant keywords, preliminary searches of scientific databases and the internet have been conducted, and guidance from the librarian at the University of Edinburgh has been sought to further refine this search strategy. The full search strategy can be seen in Textbox 3.

Textbox 3. Search strategy.

Search terms

1. *health equity/ or health services accessibility/ or socioeconomic factors/ or educational status/ or employment/ or unemployment/ or family characteristics/ or income/ or medical indigency/ or occupations/ or poverty/ or poverty areas/ or social change/ or social class/ or social conditions/ or digital divide/ or health disparity/*
2. *Age Factors/ or exp Population Groups/ or sex factors/ or rural population/ or urban population/ or developing country/ or country economic status/ or (race or racial or ethnic* or urban or rural or age factor* or elderly or seniors or (old* adj2 (age* or adult* or people or person or patient* or men or women)) or gender).ti,ab,kf.*
3. *(age factor* or cities or (countr* adj4 (low or middle or income or develop*)) or demograph* or (determinant adj2 health) or (develop* adj2 (sustainab* or millennium or countr*)) or (digital adj1 divide) or disab* or disadvantag* or discrimination or dispari* or (dominant adj2 gender) or (impair* adj1 (visual* or hear*))).mp.*
4. *(economic* or (education* adj2 (status or attain* or level*)) or employment or equit* or ethnic* or gender or geograph* or housing or homeless* or illitera* or income or inequit* or last mile or (last adj1 mile) or literacy or literate or location or marginali* or migrant* or immigrant* or (minority adj2 (cultur* or religio* or ethnic* or racial)) or poor or poverty or race or racial or rural or (social adj1 (class or status)) or socioeconomic* or stigma or underserved or undocument* or unemploy* or vulnerable or wom#n).mp.*
5. Terms 1 *or* 2 *or* 3 *or* 4
6. *(co-creation or (co adj1 (creation or design)) or community based participatory research or community-based participatory research or (design adj2 (thinking or human or cent* or inclusive or participatory or service or user or experience or communit*))).mp.*
7. *universal design/ or design for all/*
8. Terms 6 *or* 7
9. *telemedicine/ or telehealth/ or artificial intelligence/ or machine learning/ or medical informatics/ or electronic health records/ or mobile applications/ or exp Informatics/*
10. *(artificial intelligence or digital health or e-health or ehealth or m-health or mhealth or (digital adj2 (health or solution* or system*)) or (health adj2 (electronic or record* or tele* or medical)) or ict4d or (information adj5 development) or machine learning or mobile health or telecare or telehealth or telemedicine or tele-health or teleconsultation or tele-consultation or tele-care or tele-medicine or (tele adj1 (medicine or care or health or consultation)) or ((virtual* or remote*) adj4 (visit* or consult* or meet* or appoint* or communicat*)) or (Health* adj4 tech*) or e-portal* or eportal* or (Patient* adj2 portal*) or (medical adj2 informatic*)).mp.*
11. Terms 9 *or* 10
12. Terms 5

    and 8 *and* 11

Selecting Studies

In order to select relevant studies, inclusion and exclusion criteria have been developed, as shown in Table 1. These criteria are structured according to the domains put forward by the Joanna Briggs Institute [37,39], which are "population," "concept," "context," and "type of evidence." The domain "other variables" has been added to capture language, date, and format criteria.

Although gray literature will be included in this scoping review, only 2 databases (ProQuest Dissertations and Theses and Global Index Medicus) will be searched. We acknowledge that this may prevent us from finding relevant data sources regarding human-centered design that may have been published as white papers or through more informal channels, such as blog posts or forums. However, we think that this is necessary to keep the number of articles under consideration manageable. On the other hand, the ACM Digital Library—the largest database for computing and information technology literature—has been included to widen the scope beyond health-related databases only. Additionally, it was decided that the cutoff date for inclusion will be 2009, as it is mostly after the early 2000s that digital health started to be more widely applied [43].

After removing duplicate studies, title screening will be done first. Studies that do not provide enough information in the title, along with those that appear to meet the inclusion criteria, will move forward to abstract screening. During abstract screening, the same approach will be taken, so that studies with abstracts that do not have enough information for determining if they meet the inclusion criteria will move forward to full-text screening along with those that clearly meet the inclusion criteria. Finally, full-text screening will be performed.

Two authors (LE and JE) will carry out screening. When consensus cannot be achieved regarding the exclusion or inclusion of specific studies, a third author (KK or CP) will screen the text to break the tie. Covidence software [44] will be used, as it provides a convenient workflow for screening and data extraction when working with multiple authors.

Table 1. Inclusion and exclusion criteria structured according to the "population," "concept," "context," and "type of evidence" domains suggested by the Joanna Briggs Institute [37,39].

Domain	Inclusion criteria	Exclusion criteria
Population	• Any population	• N/A[a]
Concept	• Focus on design in digital health that shows a direct (explicitly addresses health equity) or indirect (addresses related concepts such as the ones listed in the search strategy) impact on health equity • Design methodology is used to develop or refine a digital health tool that is deployed at least to the pilot stage	• Focus on digital health without evidence of a direct or indirect impact on health equity (eg, exclusively concerned with the impact on usability) • Design methodology is not used to develop or refine a digital health tool that is deployed at least to the pilot stage (eg, design is used to establish the feasibility of creating a digital tool only)
Context	• Any geographical or social context	• N/A
Types of evidence sources	• Peer-reviewed articles of any design • Gray literature	• Abstracts only • Books • Systematic literature reviews, scoping reviews, or protocols
Other variables	• Published in English or Spanish • Studies published on or after 2009 • Full article is available digitally	• Published in any language other than English or Spanish • Studies published before 2009 • Full article is not available digitally

[a]N/A: not applicable.

Charting the Data

Once relevant articles have been selected, data will be extracted into the categories suggested by the Joanna Briggs Institute (Textbox 4). In an initial pilot step, 3 to 5 studies will be chosen, and relevant information will be extracted to understand if other categories for data extraction should be added.

Textbox 4. Joanna Briggs Institute key categories for data extraction [39].

Categories

1. Author(s)
2. Year of publication
3. Origin/country of origin (where the source was published or conducted)
4. Aims/purpose
5. Population and sample size within the source of evidence
6. Methodology/methods
7. Intervention type, comparator, and details of these (eg, duration of the intervention)
8. Outcomes and details of these (eg, how measured)
9. Key findings that relate to the scoping review questions

Ethics Approval

As required, our scoping review has obtained approval from the University of Edinburgh Ethics Committee. Because scoping reviews use secondary data, no further ethics approval is needed; however, we will review selected literature to ascertain whether they conducted their research according to ethical guidelines. The previously stated methodology establishes a transparent and reproducible search strategy and study selection inclusion criteria, which limit the potential for personal bias [45].

Results

As of March 2022, a preliminary search of the peer-reviewed databases has yielded over 4900 studies, and more are anticipated when gray literature databases are searched. We expect that after duplicates are removed and screening is completed, a much smaller number of studies will meet all of our inclusion criteria. The results will be presented using a 2-fold approach. First, we will present a numerical overview of the amount and kinds of studies and the key themes of the studies. Second, we will write a narrative synthesis based on the evidence extracted.

Discussion

Study Implications

For our review, we will search for and analyze the research literature on health equity, digital health, and human-centered design that is available to date, with the aim of understanding

how human-centered design approaches in digital health may have an impact on health equity. One of the anticipated findings is the misuse of the concept of human-centered design, as it is likely that in many instances, the concept is used just to define user requirements or evaluate usability instead of being applied as an overall guide for implementation (ie, from the planning stage to the final stages of scale-up and evaluation). At the core of our study, there is a desire to disseminate the findings as widely as possible among the digital health community, implementers, and researchers alike, in the hope that such findings can contribute to the better understanding of the role that design in digital health has in health equity. In turn, such understanding could translate into action that leads to stronger, more equitable health care systems.

Conclusions

Although there has been much discussion about the importance of design for lowering barriers to digital health participation, the evidence base demonstrating its impacts on health equity is less obvious. As the digital health, design, and health equity fields continue to gain prominence in the sphere of health across all settings, we believe that scoping and analyzing the existing literature will be a useful exercise that will shed more light on the equity impact of digital health design practices.

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Authors' Contributions

LE authored and led the development of the protocol. JE provided guidance and continuous feedback on the topic and methods. CP and KK provided feedback on the topic and methods.

Conflicts of Interest

None declared.

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Abbreviations

PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Technology-Based Interventions in Substance Use Treatment to Promote Health Equity Among People Who Identify as African American/Black, Hispanic/Latinx, and American Indian/Alaskan Native: Protocol for a Scoping Review

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Abstract

Background: Technology-based interventions (TBIs; ie, web-based and mobile interventions) have the potential to promote health equity in substance use treatment (SUTx) for underrepresented groups (people who identify as African American/Black, Hispanic/Latinx, and American Indian/Alaskan Native) by removing barriers and increasing access to culturally relevant effective treatments. However, technologies (emergent and more long-standing) may have unintended consequences that could perpetuate health care disparities among people who identify as a member of one of the underrepresented groups. Health care research, and SUTx research specifically, is infrequently conducted with people who identify with these groups as the main focus. Therefore, an improved understanding of the literature at the intersection of SUTx, TBIs, and underrepresented groups is warranted to avoid exacerbating inequities and to promote health equity.

Objective: This study aims to explore peer-reviewed literature (January 2000-March 2021) that includes people who identify as a member of one of the underrepresented groups in SUTx research using TBIs. We further seek to explore whether this subset of research is race/ethnicity conscious (does the research consider members of underrepresented groups beyond their inclusion as study participants in the introduction, methods, results, or discussion).

Methods: Five electronic databases (MEDLINE, Scopus, Cochrane Library, CINAHL, and PsycInfo) were searched to identify SUTx research using TBIs, and studies were screened for eligibility at the title/abstract and full-text levels. Studies were included if their sample comprised of people who identify as a member of one of the underrepresented groups at 50% or more when combined.

Results: Title/abstract and full-text reviews were completed in 2021. These efforts netted a sample of 185 studies that appear to meet inclusionary criteria. Due to the uniqueness of tobacco relative to other substances in the SUTx space, as well as the large number of studies netted, we plan to separately publish a scoping review on tobacco-focused studies that meet all other criteria. Filtering for tobacco-focused studies (n=31) netted a final full-text sample for a main scoping review of 154 studies. The tobacco-focused scoping review manuscript is expected to be submitted for peer review in Spring 2022. The main scoping review data extraction and data validation to confirm the accuracy and consistency of data extraction across records was completed in March 2022. We expect to publish the main scoping review findings by the end of 2022.

Conclusions: Research is needed to increase our understanding of the range and nature of TBIs being used in SUTx research studies with members of underrepresented groups. The planned scoping review will highlight research at this intersection to promote health equity.

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KEYWORDS

health disparities; scoping review; social determinants of health; substance use; treatment; technology-based interventions; underrepresented

Introduction

Pervasive inequalities known as health disparities arise when disease incidence, prevalence, morbidity, mortality, or survival is worse in a population subgroup than in the general population. Health and health care are strongly influenced by race and ethnicity, socioeconomic status (SES), and other characteristics, which can impact access to quality health care. Health disparities have produced negative social and economic consequences on a national scale in the United States [1]. Historically, health treatment intervention research has infrequently been conducted with people who identify as a member of one of the underrepresented groups as a principal focus; this is equally true for the substance use and substance use disorder (SUD) treatment (SUTx) field [2]. A general lack of attention to issues of access, inclusion, retention, equity in outcomes, and culturally relevant research are sources of disparities in substance use (and related consequences) for members of underrepresented groups [3]. Fortunately, there is a small but growing body of literature of best practices for researching diverse groups that may serve as a guide for those motivated to better understand how to reduce health disparities [4] and more equally distribute benefits across populations [5].

Technology-based interventions (TBIs) for SUTx show great promise for expanding reach, providing access to high-quality, personalized, evidence-based treatments (EBTs), while reducing barriers to treatment [6] (eg, access, adoption/uptake, adherence, effectiveness [1], or cultural appropriateness/relevance of TBIs [7]). The rapid proliferation of TBIs has revolutionized clinical and research practices, and these fields will continue to grow rapidly and have a substantial impact on population health [2]. However, there are legitimate concerns that these promising technological advances can lead to unintended consequences such as perpetuating health and health care disparities for people who identify as African American/Black, Hispanic/Latinx, and American Indian/Alaskan Native [8]. Describing common goals of researchers in the health research community when trying to improve well-being, the thinking is that the worst thing that could happen is that our efforts have no effect. However, there is a real and more insidious possibility: that our technological interventions do work but that they work better for those who are already privileged, creating intervention-generated inequalities [1].

People who identify as members of underrepresented groups comprise over one-third of the admissions to publicly funded SUTx programs [9]; however, recent research suggests these individuals may be at particular risk for poor treatment outcomes, due in part to socioeconomic factors [10] and racism [11,12]. Despite socioeconomic challenges, the digital gap among members of underrepresented groups and Caucasian individuals has narrowed over the past 15 years [13]. Technology-based interventions for substance use and SUDs show substantial promise for providing access to high-quality EBT. Increased understanding of the use of TBIs in the field of SUTx with directed attention to how technology may reduce health disparities/promote health equity, or can be harnessed to do so, is warranted.

Given the indications for our literature synthesis—*to identify key characteristics or factors related to a concept* and *to examine how research is conducted on a certain topic*—a scoping review is deemed the most appropriate method [14]. A preliminary search of MEDLINE, the Cochrane Database of Systematic Reviews, and *JBI Evidence Synthesis* was conducted, and no current or underway systematic reviews or scoping reviews on the topic were identified.

This scoping review aims to characterize the range and nature of TBIs being used in SUTx research studies with a majority of people who identify as African American/Black, Hispanic/Latinx, and American Indian/Alaskan Native. Most interventions lack the inclusion of vulnerable/underrepresented populations, which contributes to limited generalizability and the meaningful use of TBIs for improving community health, further perpetuating health disparities [15]. Thus, by identifying and comparing published interventions that *include* such groups, we are taking the first step to interrupt the perpetuation of disparities by attending to access (recruitment/retention); equity in outcomes (evaluations of health changes related to use of the TBI; eg, tobacco cessation); evaluation of the technology itself, such as the usability and helpfulness; and the cultural relevance of the research (multicultural approach vs generalizability approach) [4].

Additionally, we aim to identify and examine the race/ethnicity consciousness of studies included in this review, meaning that if a study considers underrepresented groups, beyond their inclusion as study participants, in the introduction, methods, results, or discussion, it will be considered race/ethnicity conscious (Textbox 1). By taking this further step to explore the extent to which these studies that include members of underrepresented groups are explicit about race or ethnicity and the impacts of TBIs for particular people (because intervention outcomes from one group do not necessarily generalize to other groups [16]), we further highlight research efforts to promote health equity. We believe that by identifying the studies that

are race/ethnicity conscious and examining the content of the portions of the manuscript (methods, analytic plan, discussion, or interpretation of results) that meet that criterion, we will be able to provide substantive insight into how people who identify as members of underrepresented groups are included in sociotechnical TBI development, recognizing the interrelatedness of the social and technical factors in particular environments creating optimal tools to enhance well-being [17]. Finally, we plan to summarize findings from race conscious studies that underscore insights that may help other researchers design or adapt designs such that the effects for members of underrepresented groups promote health equity. Importantly, the identification of included studies that are not found to be race conscious may still yield substantial insights and substantive knowledge about how these communities are affected by the use of TBIs for SUTx.

Textbox 1. Race/ethnicity conscious research practices in manuscripts.

If a study includes reference to race or ethnicity in one or more sections of their manuscript it will be considered race/ethnicity conscious. Examples of race/ethnicity conscious studies are those that:

Introduction

- Mention one or more racial or ethnic groups in the literature review or enlist a theory that is described as one that may help address health disparities among racial/ethnic/underrepresented groups. An example of this includes sociological trust theory—bridge between broad lens of culturally informed design and attention to trust or distrust.

Methods

- Plan for health equity focused analyses by powering studies for subgroup analyses or analyses of effect modifiers while following rigorous standards for heterogeneity of treatment effect analyses or use race or ethnicity as a covariate in analyses, or in some other way consider race in the plan for analyzing the data. Race conscious methods may also include references to recruitment or retention efforts aimed at racial or ethnic groups such as cultural tailoring of materials or consideration of matching staff race/ethnicity to that of the sample participants.

Results

- Present findings in a way that highlights differences/similarities for members of different racial and/or ethnic groups

Discussion

- Interprets findings for members of racial or ethnic groups by locating results in the context of other development or treatment literature

Methods

Scoping Review

This review will adhere to the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) guidelines, including search strategy, selection criteria, data extraction, and analysis [18]. Additionally, the review will be conducted using the Arksey and O'Malley [19] methodological framework for scoping reviews that recommends the following six steps: (1) identifying the research question; (2) identifying relevant studies; (3) study selection; (4) charting the data; (5) collating, summarizing, and reporting results; and (6) consultation. The review will be reported according to PRISMA-ScR (PRISMA Extension for Scoping Reviews) guidelines [20]. This scoping review was initiated in January 2021 and is expected to be completed by the end of 2022.

Step 1: Identifying the Research Question

The following research question was identified to guide the scoping review: Does the use of digital TBIs in SUTx research promote health equity among people who identify as African American/Black, Hispanic/Latinx, and American Indian/Alaskan Native?

To increase clarity and focus needed to inform subsequent phases of the research process, we operationally defined health equity as the inclusion of members of underrepresented groups (previously specified) in research of TBIs for substance use, as well as the extent to which the research is race/ethnicity conscious. Thus, the following questions are intended to establish an effective search strategy [16]:

- Does research enlisting TBIs in SUTx include people who identify as African American/Black, Hispanic/Latinx, or American Indian/Alaskan Native?
- If the substance use research enlisting TBIs does include people who identify as African American/Black, Hispanic/Latinx, or American Indian/Alaskan Native, is it race/ethnicity conscious?

Population

The focus of this review is on the following racial and ethnic groups: African American/Black, Hispanic/Latinx, and American Indian/Alaskan Native. The former two groups are included as they are the largest racial and ethnic groups underrepresented in SUTx in the United States [21]. People who identify as African American/Black and Hispanic/Latinx have been found to be less likely to complete treatment compared to Caucasian individuals [22,23] for a variety of reasons such as disproportionately lower SES [10], greater likelihood of incarceration [24], lower perceived treatment efficacy, and cultural factors [25]. The review also focuses on people who identify as American Indian/Alaskan Native, as members of this group of Americans have the highest rates of substance use problems compared with members of other groups, and access to care remains extremely limited [26,27].

Concept

Technology-based interventions are used as an umbrella term that encompasses interventions such as mobile-based interventions, computer-based interventions, and web-based interventions. The term TBIs was selected because it encompasses a broad array of platforms, including the computer, internet, social media, and mobile apps [28].

Context

Eligible papers describe the use of TBIs that facilitate the inclusion of members of underrepresented groups in SUTx or support delivery of SUTx to members of underrepresented groups. Examples of potential TBIs used to support SUTx are interactive voice response (IVR) and ecological momentary assessments. Substance use treatment defined for this review includes treatment for any type of SUD, including alcohol, tobacco, and other drugs; treatment for substance use that does not meet disorder criteria yet is still considered risky, problematic, or heavy use; treatment provided in any type of setting (inpatient or outpatient settings); treatment provided to both individuals and people in group settings; and treatments that are both evidence-based with rich supporting literature (ie, medication-assisted treatments including pharmacotherapies such as naltrexone, methadone, buprenorphine), behavioral or psychological therapies (brief interventions, cognitive behavioral therapy, contingency management, drug counseling, motivational interviewing), and integrated psychotherapy and pharmacotherapy, as well as newly designed treatments that are being presented in pilot/efficacy studies. Importantly, assessment, or the process of obtaining information about a participant's drug use and how it affects their life, is considered an integral part of treatment, and therefore, studies that focus on assessment or monitoring impacts of use with a focus on reduced use or cessation/abstinence are also included.

Step 2: Identifying Relevant Studies

Information Sources and Search Strategy

Before enlisting the help of Dartmouth College research librarians, study team members conducted preliminary independent literature searches in PubMed and Google Scholar using search terms associated with the three domains of interest: TBIs, SUTx, and sample inclusion of members of underrepresented groups. This step netted dozens of research studies that appeared to meet the inclusion criteria. Further, we reviewed the reference lists of these studies (examining titles and abstracts) for additional literature, identifying many additional studies that appeared to meet our inclusion criteria. Based on this preliminary literature search, we believed there would be ample evidence that met our search criteria and therefore elected to only include US-based peer-reviewed studies. Further underscoring the rationale for limiting our focus on US studies, underrepresented groups in the United States differ from underrepresented groups in other countries.

The search strategy aimed to locate published peer-reviewed studies based on the preliminary data analysis. An initial limited search of MEDLINE was undertaken to identify studies that met selected criteria. Search terms were organized by two of the domains of interest: TBIs and SUTx. However, the target race and ethnicity demographics were not included in this search strategy. Rather, team members manually reviewed for this criterion at the title/abstract and full-text level because the wide variation in search terms used to identify sample makeup based on race and ethnicity may inadvertently eliminate eligible studies.

The text contained in the titles and abstracts of relevant studies, and the index terms used to describe the studies, was used to develop a full search strategy for MEDLINE, Scopus, Cochrane Library, CINAHL, and PsycInfo (see Multimedia Appendix 1). The search strategy, including all identified keywords and index terms, was adapted for each included database or information source.

This scoping review was conducted by nine researchers from a variety of disciplines at Dartmouth College. This larger group was split into three smaller clusters to complete blinded decisions on each study at the title/abstract and full-text review phases. Additionally, these groups conducted data extractions from each included study.

Step 3: Study Selection

Types of Sources

We considered peer-reviewed, qualitative, quantitative, and mixed methods studies. Study designs include but are not limited to randomized trials, randomized controlled trials (efficacy/effectiveness), feasibility/acceptability pilots, formative development, secondary analyses (eg, mechanisms or moderators), and assessments.

Eligibility Criteria

Eligible studies are US-based, English language, peer-reviewed, published between January 2000 and March 2021, include participants 12 years and older (average age of onset of substance use), and 50% or more of the sample represents individuals who identify as African American/Black, Hispanic/Latinx, or American Indian/Alaskan Native when combined. While most people who identify as Hispanic/Latinx also identify as White/Caucasian, identification as Hispanic/Latinx is the prioritized category and takes precedence over race given that most studies do not report race stratified by ethnicity. When calculating the 50%, we do not include categories of *other* or *multi-race*, as they are too vague to help address the scoping review's aims. We chose this 50% threshold after reviewing the guidance of a research review on EBT for ethnic minority youth. To evaluate treatments for ethnic minority youth, Huey and Polo [29] suggested that an intervention could be considered well-established, probably efficacious, or possibly efficacious for ethnic minority youth if supporting studies met one or more of three conditions: (1) at least 75% of participants were ethnic minorities, (2) if either separate analyses with the subset of ethnic minority participants demonstrated superiority of treatment over control/comparison conditions, or (3) analyses showed ethnicity did not statistically moderate treatment outcomes. We decided to use 50% to be more inclusive and capture additional studies. Additionally, eligible studies include a TBI integrated into SUTx.

Exclusion Criteria

Studies were excluded if they are conducted outside of the United States or published outside of the study window (January 2000 to March 2021). Furthermore, we removed protocol papers, as well as papers that detail the work researchers plan to perform in the future. Other papers that are not included in the final list are reviews, commentaries, editorials and opinion pieces, student theses, book chapters, and guidelines. Additionally, we excluded studies solely focused on mental health, pharmacological, cost evaluations, telephone counseling (eg, tobacco quitlines), and primary prevention interventions.

Screening and Selection Procedure

Following the search, all netted citations were uploaded by the research librarians into Endnote X9 (Clarivate Analytics), a citation management software program, to manage references and remove duplicates [30]. To facilitate study screening and selection, all citations obtained using the search strategy were imported into Rayyan, a web-based tool used to assist researchers in screening, selecting, and labeling studies for systematic reviews [31]. Rayyan was used to blind individual reviewers on each of the three teams to individual team member's decisions regarding inclusion/exclusion of each study. This process was used at both the title/abstract and full-text review level. Once citations were mutually agreed upon by team members and therefore included, potentially eligible studies were retrieved in full and their citation details imported into Rayyan. The full text of selected citations was assessed in detail against the inclusion criteria by two or more independent reviewers on each of the three teams. Reasons for exclusion of sources at the full text stage will be recorded and reported in the scoping review. Examples of this include international studies, studies that did not meet sample criteria, and wrong publication type. Any disagreements that arose between the reviewers at each stage of the selection process were resolved through discussion or with additional reviewers.

Step 4: Charting the Data

Data Extraction

Data were extracted from included studies by our team of nine independent reviewers using a standardized data extraction tool built into Excel (Microsoft Corporation; see Multimedia Appendix 2) over approximately 6 months. We extracted basic study information including first author, year of publication, and study aims/purpose. In addition, we extracted population, design, sample (racial and ethnic profile), details related to the TBI, substances that are the focus of the TBI, main outcomes, and key findings that relate to the scoping review questions regarding race and ethnicity consciousness. Reviewers were divided into three teams to pilot the extraction form on three studies. The entire nine-person team met to discuss issues arising during the pilot experience, refine procedures, and revise the form. The extraction process was iteratively modified as necessary throughout the conduct of the scoping review and will be detailed in the scoping review outcomes paper. Any disagreements that arose between the reviewers were resolved through discussion or with additional reviewers. Throughout the data extraction process, methodical quality checks were conducted to ensure the consistency, accuracy, and thoroughness of the information extracted. In one instance, the authors of a research program that included several studies eligible for our review were contacted to request additional data.

Step 5: Collating, Summarizing, and Reporting the Results

Data Analysis and Presentation

Evidence presented in our review will directly respond to the review objectives and questions, and will be presented in tabular form. First, we will characterize the included studies by author, year of publication, aims, design, sample, population, and substance. Second, we will characterize the TBIs being used in SUTx research with members of underrepresented groups. Third, we will examine how SUTx research with people who identify as African American/Black, Hispanic/Latinx, and American Indian/Alaskan Native using TBIs is being conducted, highlighting studies that exemplify race/ethnicity conscious research practices throughout their published manuscripts that may promote health equity. We will also provide a narrative summary of the tabulated results and describe how the results relate to the review's questions and aims.

Step 6: Consultation

No patients were involved in the design of this scoping review. Experts with experience conducting scoping reviews as well as conducting research using TBIs with underrepresented groups may be consulted in the presentation of findings for this scoping review.

Results

The title and abstract review was completed in 2021, netting 6897 articles. Following the exclusion of 5615 records not meeting study inclusion criteria, a full-text review was conducted on 1158 records over a 3-month period. Following the exclusion of 935 full-text records for four primary reasons—race/ethnic criteria not met (n=486), wrong publication type (eg, conference abstract; n=181), not a US-based study (n=161), or not a TBI (n=89)—185 records remained. We plan to publish the full PRISMA diagram with the main scoping review. Notably, due to the uniqueness of tobacco relative to other substances in the SUTx space [32], as well as the large number of studies netted, our team made the decision to separately publish a scoping review on tobacco-focused studies that meet all other criteria. Filtering for tobacco-focused studies (n=31) netted a final full-text sample for a main scoping review of 154 studies. The tobacco-focused scoping review manuscript is expected to be submitted for peer review in spring 2022. The main scoping review data extraction is completed. By March 2022, data validation to confirm the accuracy and consistency of data extraction across records will be completed, and we expect to publish the main scoping review findings by the end of 2022.

Discussion

Potential Impact and Future Directions

The proposed scoping review will have the potential to provide a status update on TBIs for SUTx and their potential to promote health equity among people from historically underrepresented groups. By identifying the universe of US-based studies on TBIs for SUTx that include people who identify as African American/Black, Hispanic/Latinx, and American Indian/Alaskan Native in the past 20 years, this review will likely provide guidance on how researchers and developers may avoid worsening inequities through increasing the race/ethnicity consciousness of both research practices and technological innovations. By identifying research on TBI use in SUTx that include members of underrepresented groups, we anticipate the main findings to include insights into issues of participant access to research on TBIs (eg, the prevalence of one group's representation in the netted review's sample compared with that of others highlighting research gaps, recruitment and retention strategies, incentive structures, or platform access descriptions), the main types of TBIs being used with members of these groups (eg, IVR, SMS text messages, computer-delivered, smartphone, social media, or virtual reality), the cultural relevance or lack thereof (end-user engagement) of the TBIs under study, the relative efficacy of certain TBIs versus comparators, and an in-depth understanding of the extent of the race consciousness of the netted sample of studies included in the review. While there is no prior work on this specific niche of the literature, several other published scoping reviews at the intersection of TBIs and health inequities may be of interest to readers [33,34].

As the landscape of SUTx evolves and as underrepresented groups grow (eg, migration) in the United States, this review may become more pertinent for TBI SUTx researchers in particular. The results of the search and the study inclusion process will be reported in full in the final scoping review, published in a peer-reviewed journal, and presented in a PRISMA-ScR flow diagram [35]. This protocol is designed to highlight our methods, facilitate replication, alert researchers to the fact that the review is being conducted [14,35], and forecast anticipated findings.

Limitations

By limiting inclusion in the scoping review to studies with 50% of the sample comprised of the three race/ethnicity categories, we recognize that we may unnecessarily limit the sample of studies for inclusion in the scoping review. However, we chose this threshold after reviewing the guidance of an article that summarized research on EBT for ethnic minority youth that suggested that an intervention could be considered possibly efficacious for ethnic minority youth if at least 75% of participants were ethnic minorities [29]. In choosing the less conservative number of 50%, we planned to be more inclusive. Relatedly, by limiting our inclusion criteria to studies with 50% of the sample comprised of the three race/ethnicity categories, we exclude studies that may have findings for mixed race or ethnicities. It has also come to our attention that it might have been useful to consider studies where the initial recruitment included a substantial proportion of participants who identified as one of the underrepresented groups but not necessarily in the final sample. Inclusion of such studies might have helped to identify shortcomings in study design that inadvertently exclude these individuals that would have contributed to the scoping review's goal to inform equity impacts of TBIs. We also recognize that limiting our scoping review to the English language and only US studies is common in systematic reviews and could result in biased interpretation of findings [36]. However, the research team lacks fluency in additional languages, limiting our ability to conduct a review beyond an English-only data set. A suggestion for future research will include a recommendation to broaden the language criteria beyond English, particularly to include Spanish and Native language studies given the focus of this review on the impact of TBIs for SUTx for individuals who identify as African American/Black, Hispanic/Latinx, and Native American/Alaskan Native. Additionally, while we will use several databases, there is the possibility that we have overlooked some relevant research that meets our search criteria.

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Conflicts of Interest

LAM is affiliated with Square2 Systems and Pear Therapeutics. These relationships are extensively managed by her academic institution, Dartmouth College. The other authors report no financial relationships with commercial interests.

Multimedia Appendix 1
Medline (Ovid). Database(s): Ovid MEDLINE and Epub Ahead of Print, In-Process, In-Data-Review, and Other Non-Indexed Citations and Daily 1946 to March 29, 2021.
[DOCX File , 14 KB - resprot_v11i5e34508_app1.docx]

Multimedia Appendix 2
Data extraction items.
[DOCX File , 15 KB - resprot_v11i5e34508_app2.docx]

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Abbreviations

EBT: evidence-based treatment
IVR: interactive voice response
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
SES: socioeconomic status
SUD: substance use disorder
SUTx: substance use treatment
TBI: technology-based intervention

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Protocol

Pedagogical Approaches and Learning Activities, Content, and Resources Used in the Design of Massive Open Online Courses (MOOCs) in the Health Sciences: Protocol for a Scoping Review

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Abstract

Background: Developing online, widely accessible educational courses, such as Massive Open Online Courses (MOOCs), offer novel opportunities to advancing academic research and the educational system in resource-constrained countries. Despite much literature on the use of design-related features and principles of different pedagogical approaches when developing MOOCs, there are reports of inconsistency between the pedagogical approach and the learning activities, content, or resources in MOOCs.

Objective: We present a protocol for a scoping review aiming to systematically identify and synthesize literature on the pedagogical approaches used, and the learning activities, content, and resources used to facilitate social interaction and collaboration among postgraduate learners in MOOCs across the health sciences.

Methods: We will follow a 6-step procedure for scoping reviews to conduct a search of published and gray literature in the following databases: Medline via Ovid, ERIC, SCOPUS, Web of Science, and PsychINFO. Two reviewers will screen titles, abstracts, and relevant full texts independently to determine eligibility for inclusion. The team will extract data using a predefined charting form and synthesize results in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews checklist.

Results: The scoping review is currently ongoing. As of March 2022, we have performed initial data searches and screened titles and abstracts of the studies we found but revised the search string owing to inaccurate results. We aim to start analyzing the data in June 2022 and expect to complete the scoping review by February 2023.

Conclusions: With the results of this review, we hope to report on the use of pedagogical approaches and what learning activities, content, and resources foster social and collaborative learning processes, and to further elucidate how practitioners and academics can harvest our findings to bridge the gap between pedagogics and learning activities in the instructional design of MOOCs for postgraduate students in the health sciences.

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KEYWORDS

MOOC; scoping review; collaborative learning; PhD; postgraduate; education; health sciences; massive open online course

Introduction

Developing online, widely accessible educational courses, such as Massive Open Online Courses (MOOCs), offer novel opportunities to advance academic research and the educational system in resource-constrained countries [1,2]. A PhD proposal or research protocol is one of the first important academic texts aspiring researchers write worldwide [3], however; there is little emphasis on developing academic writing at the postgraduate level [4,5]. To facilitate social equity in the health sciences, an accessible course focusing on PhD proposal writing could offer opportunities for students from low- and middle-income countries (LMICs) to increase their writing capacity and successfully compete for PhD scholarships and scholarly positions at research-intensive higher education institutions (HEIs) [2,6].

MOOCs are "*online* courses designed for large numbers of participants that can be accessed by anyone anywhere as long as they have an internet connection (*massive*), are *open* to everyone without entry qualifications, and offer a full/complete course experience online for *free*" [7]. As such, a MOOC brings together participants from diverse backgrounds and disciplines worldwide with a common interest to learn and coconstruct knowledge in a socially networked, nonformal, computer-mediated learning environment [8,9].

Traditionally, there are 2 main types of MOOCs depending on the pedagogical approach underpinning the design, affordances of the course platform, and the degree of openness (nonprofit or for profit) [10,11]. A cMOOC has a social learning, or connectivist approach [12]. In cMOOCs, active social interaction and collaboration is viewed as required to coconstruct knowledge as a member of an active open, online community [11,13]. Through the learning activities, "learners decide their own objectives, share their knowledge and collaboratively build their ideas and artifacts" [10]. An xMOOC uses an individual learning or cognitive behavioral approach with didactic or transmission models of teaching, with somewhat limited openness (often for profit) and less emphasis on learners' coconstruction of knowledge [10,14]. Here, the teaching methods often include information transmission, computer-marked assignments, and peer assessment [10]. Other more recent MOOCs use a blended-learning approach, also referred to as hybrid MOOCs (eg, bMOOCs and smMOOCs) combining elements from the different pedagogical approaches [11,15].

Although literature reviews have summarized the use of design-related features and principles of different pedagogical approaches [8,10,15-18], the quality of the learning experiences in MOOCs have been questioned [13,19]. Common learning activities of most types of MOOCs include video or face-to-face lectures, blogs, discussion forums, social networks, lecture notes, PowerPoint slides, and PDFs [10]. However, in cMOOCs or blended-learning MOOCs, where social interaction and collaboration is anticipated to foster key learning throughout or in parts of the course, studies have demonstrated that there are limited learning activities in which social learning *could* take place [13,19]. In addition, a review of cMOOCs and xMOOCs found that only one-third of them had material or resources, which learners viewed relevant for the learning outcome [19]. Considering the dynamic and complex individual learning process in a computer-mediated setting [9], it is important that learning activities, content, and resources reflect an a priori pedagogical approach underpinning the MOOC design, and that the materials offered are viewed by learners as helpful and relevant to achieve the stated learning objectives [13].

In this paper, we present a protocol for a scoping review aiming to systematically identify and synthesize literature on the pedagogical approaches used, and the learning activities, content, and resources used to facilitate social interaction and collaboration among postgraduate learners in MOOCs across the health sciences.

Methods

Methods Overview

We will follow the 6-step systematic procedure for scoping reviews as outlined by Arksey and O'Malley [20]. This procedure includes (a) identifying the research question; (b) identifying relevant studies; (c) selecting studies; (d) charting the data; (e) collating, summarizing, and reporting the data; and (f) an optional consultation exercise. We will also use the PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) checklist to further guide what we report in this protocol and the final review [21] while adhering to recommendations made in recent methodological scoping review papers that advance the procedure proposed by Arksey and O'Malley [22-24].

As the findings of the proposed scoping review can inform a potential revision of the MOOC *How to Write a PhD Proposal*, we account for the theoretical positioning underpinning the work to develop this MOOC and the pedagogical approach used in the design phase. The work aligns with the knowledge creation metaphor of learning, where learning is viewed "as a process of knowledge creation which concentrates on mediated processes where common objects of activity are developed collaboratively" [25]. In a computer-mediated online learning setting, such as an MOOC, an underlying principle of the knowledge creation approach to learning is that each learner's effort to advance knowledge and skills occurs in, and benefits from, participation in the social online community [25,26]. This understanding is in line with the pedagogical approach of cMOOCs and the blended learning approaches used in MOOCs. However, when embarking on developing the MOOC in PhD proposal writing, we had to adjust the thinking underlying the course design to accommodate the blended learning approach integrated in the online learning platform FutureLearn. Although we designed the key activities in accordance with the social knowledge creation approach to learning, the blended learning principles integrated in the FutureLearn platform also accommodated other ways of learning (eg, acquisition learning [25]).

Each learner who registers for the MOOC on PhD proposal writing is assumed to have a research idea, but to develop the

research idea into a plan or proposal (the common object of activity), the learners are encouraged to actively participate in the key learning activities or tasks that require social interactions and extensive collaboration with other learners (eg, reviewing the work of others together with other participants). Through these forms of feedback and collaborative work, participants could learn from others by reading the work of others and integrating key elements of PhD proposal writing into their own work.

To ensure consistency throughout this scoping review, the lead researcher will spearhead the work during each stage of the review process [27]. We will set up an iterative process to ensure a well-crafted scoping review that demonstrates procedural transparency and methodological rigor [21,22]. We are a research team with experience in conducting exploratory research and various types of literature reviews in the fields of medicine, nursing, education, and sports science. Throughout the process, we will also track refinements of the proposed protocol [22].

Identifying the Research Question

The first step of the systematic scoping review process involves identifying and defining the parameters of the research question [20]. This is usually done a priori to guide the literature searches, followed by an iterative process of refinement based on familiarization with the identified research evidence [27]. Our preliminary research question is "What are the pedagogical approaches, and the learning activities, content, and resources used to foster social interaction and collaborative learning processes when designing MOOCs for postgraduate students in the Health Sciences?" We designed our research question to be broad, to generate a large but also manageable pool of data to establish an overview of the topic investigated [20,22]. We have formulated the following subquestions to further guide our scoping inquiry:

1. What are the pedagogical approaches used to guide the design of MOOCs in the health sciences?
2. What are the learning activities, content and resources used in MOOCs to facilitate social interaction and collaboration?
3. What are the social, collaborative learning activities, content, and resources do participants report as helpful and relevant in MOOCs?

Defining and operationalizing the concepts of a review question is useful to clarify the scope [24]. It guides the subsequent phases of exploration and clarifies the final review report [28]. For this study protocol, the term "design" refers to the development phase of MOOCs preceding the online launch. We define postgraduate studies as academic studies above the master's level (eg, MA, MSc, and MPhil) or equivalent (eg, MD). As such, we refer to postgraduate students as a group of people who have completed their master's thesis or similar academic degrees. When using the phrase "PhD proposal," we refer to a research protocol's specific format, genre, and style of writing needed when developing a PhD project proposal or presenting a stringent research plan, and, as such, preparing for work that meets the requirements for writing research articles or manuscripts of project results.

Identifying Relevant Studies

Overview

The second step of the scoping review is to identify relevant literature [20]. Clear definitions and operationalization of the research question, and a specification of the inclusion criteria that underpins the search strategy are necessary [29]. However, developing the search strategy is an iterative and reflexive process that requires assessment and refinement based on both the pilot searches and the materials yielded from the searches [27]. We will start with a comprehensive and broad search including published and gray literature. In line with the search guidelines developed by Aromataris and Riitano [29], we will (i) explore published literature in electronic databases, (ii) hand-search reference lists in the identified literature, and (iii) review the table of contents in a few key journals. We will search gray literature (i) by hand-searching selected organization, government, and conference websites, (ii) using selected gray literature databases, and (iii) using online search engines.

To ensure breadth and optimize consistency of the literature searches, an experienced research librarian will build, structure, and conduct all literature searches across databases [29]. As the search may yield a wide variety of studies across both published and gray literature, we will not exclude any published literature on the basis of the study design.

Search Strategy

We will adapt a Population (or participants)/Concept/Context (PCC) mnemonic and use the Boolean logic of "AND" and "OR" to build the various searches across databases. Findings in each database and the full combination of key terms used will be registered for each individual grid. We will pilot the search strategy using a 3-step approach, which includes (a) an initial search of a key database and analyze alternative terms and index or MeSH terms used to describe the concepts and (b) search the chosen database for the keywords and index terms identified [29]. Based on the piloting of our search strategy and familiarization with the research field, we may refine or add keywords and index or MeSH terms before searching the remaining databases. We will report the full details of our searches in the electronic databases as an appendix in the main scoping review paper [21].

Our search will cover the period from 2004 to March 2022. Searching for literature before 2004 is not likely to yield relevant results since the first MOOC was launched in 2008. Written material to be included in the scoping review is, for practical and financial reasons, limited to English and the Nordic languages. Using the reference management software EndNote, we will collate and organize all studies extracted per database [30] and use the integrated algorithm in EndNote to screen for duplicate references [31]. One reviewer will then carry out an initial screening of all references identified in the literature search to exclude clearly irrelevant studies; for example studies or reports emphasizing online courses targeting children, primary school students, or high school students. If the reviewer has any doubt about whether to exclude a study or report, it will

be included for further scrutiny by other reviewers at a later stage.

Electronic Databases

We will search the multidisciplinary electronic databases (eg, SCOPUS) illustrated in Table 1. Some electronic databases have a somewhat similar interface but index subject headings differently. The research librarian will tailor our search of each database to include the specific subject headings listed.

Table 1. A preliminary overview of electronic databases for the published literature search.

Name	Scope
Education Resources Information Centre	International literature database within pedagogy
Medline via Ovid	Medicine, nursing, dentistry, biomedical research
Web of Science	Cross-disciplinary, international database with mainly articles
SCOPUS	Large bibliographic database containing abstracts and citations for academic journal articles (peer-reviewed journals in medical, technical, and social sciences, including the arts and humanities)
PsycINFO via OVID	Centered on psychology and the behavioral and social sciences

Hand-Searching Reference Lists and Key Journals

We will investigate the bibliographies of literature findings and the table of contents in a few key journals that publish studies on pedagogical practices and instructional designs in MOOCs for additional relevant papers. A special emphasis is on ensuring that we also select journals that are not well indexed in available commercial or public databases to avoid missing out on potentially eligible studies [32].

Gray Literature

Searching for gray literature in repositories that specifically target this form of literature is useful to ensure breadth and limit the publication bias in literature reviews [32]. We define gray literature as conference proceedings and literature produced at all levels of government, academic, business, and industry, available in electronic and printed formats not controlled by commercial publishing houses. This includes any paper or study not formally published or peer reviewed; that is, reports, working papers, theses and dissertations, conference posters and presentations, unpublished protocols and guidelines, market reports, government documents, and white papers [33].

We will search a selection of the gray literature databases illustrated in Table 2. As these repositories may not have advanced search modes, we will use a few carefully selected critical key terms from our search grid [29]. To ensure comprehensiveness, we will also search the unpublished literature on the internet using online search engines, such as Google, in their incognito, advanced search mode with a stringent search query based on the terms used in the search string. Using relevance filtering, we will further limit the assessment to the first 50 hits per combination of key terms [34]. We will list the potential findings using EndNote [27].

Synthesizing gray literature and gray data in a systematic way is a difficult task [35]. To ensure replicability, we will list the findings from each stringent combination of key terms used in each database and add as an appendix to the main review paper.

Table 2. A preliminary overview of electronic gray literature databases for the literature search.

Name	Scope
Open-Grey	An open access gray literature database that includes technical or research reports, doctoral dissertations, some conference papers, some official publications, and other types of gray literature. OpenGrey covers Science, Technology, Biomedical Science, Economics, Social Science, and Humanities
ProQuest Dissertations and Theses	ProQuest has one of the largest collections of electronic theses and dissertations available worldwide
Google Scholar	International database that indexes the full text or metadata of scholarly literature across an array of publishing formats and disciplines, including educational science

Study Selection

The third step of the scoping review is an iterative assessment of the identified literature using the defined eligibility criteria [20,21]. A flowchart will illustrate the selection process of the literature [21]. It will specify the number of duplicates that are removed and the references excluded on the basis of either the title or abstract or the full text [34].

We will include all studies that report on conceptual or theoretical frameworks or pedagogical approaches used to guide design considerations; selection or structuring of content, learning activities, and resources that are assumed to stimulate

social interaction and collaboration; or participant views of learning material anticipated to foster social learning in cMOOCs and hybrid MOOCs. We will exclude studies or reports that describe learning material, content, or resources in xMOOCs or comparisons of online learning platforms, grading, or assessment of learner achievements, or outcome or operational or technical issues (eg, weekly supervision of courses and considerations during the launch of MOOCs), as well as studies that target participants at the undergraduate level at HEIs.

We will review studies using an iterative 2-step approach [24]. The first step involves importing all references into the app-based literature review program Covidence to screen the title and abstract in accordance with inclusion or exclusion criteria. To do so, we will hold team meetings at the beginning, midpoint, and end to discuss progress as well as any challenges and uncertainties (the number of references identified dictates the number of meetings required) related to study inclusion. If necessary, the search strategy will be refined. The second step involves the full reading of the retained studies and reports to decide on final inclusion. We will first extract the references from Covidence back into EndNote to acquire the full-text version of the studies or reports before the references are imported back to Covidence for the full read.

During the study selection process, two reviewers will screen titles, abstracts, and relevant texts independently to determine eligibility for inclusion in this scoping review [21,24]. If the first reviewer chooses to include a reference, the second reviewer will verify his or her selection of the specific study. If there are divergences between reviewers, a third reviewer will be consulted.

We will use the Mixed Methods Appraisal Tool (MMAT) to appraise the quality of the published literature identified [36]. The MMAT tool includes an extensive assessment procedure of qualitative, quantitative, and mixed methods studies. To appraise the quality of gray literature, we will use the AACODS (Authority, Accuracy, Coverage, Objectivity, Date and Significance) checklist [37]. We will not perform a full assessment of methodological robustness as we argue that it is more important and appropriate for a scoping review to capture breadth in the literature rather than a limited sample of methodological quality-assessed studies used for systematic reviews.

Data Charting

The fourth step of the scoping review process entails organizing and synthesizing the data in accordance with key themes [20]. Based on initial discussions, the research team plans to extract and chart a mixture of general information about the studies or reports in this scoping review. More specifically, we will extract the names of the authors, year of publication, study location, type of document source, aims, and any assessments of target groups or participants. Underpinned by the knowledge creation approach to learning, we will extract specific information from each study and report related to conceptual or theoretical frameworks and pedagogical approaches; selection or structuring of social, collaborative learning activities, content, and resources; and participant evaluations of any material viewed as helpful in cMOOCs or hybrid MOOCs to stimulate interaction and collaboration.

We will develop a predefined Microsoft Excel data charting form. Refinement of the charting form may be necessary, as data extraction is an iterative process involving continual assessment, evaluation, and updating [34]. To ensure consistent data extraction, the lead researcher will undertake a pilot of the form on a random sample of 5-10 studies. In consultation with the full research team, we will modify, if necessary, to mitigate inconsistencies and uncertainties of use to ensure coherence with the research question [24,27].

Collating, Summarizing, and Reporting the Results

The fifth phase of the scoping review process entails summarizing and reporting findings in a clear and consistent way [20]. Throughout the reporting phase, we will follow the recommendations of the PRISMA-ScR guidelines when writing up the final review [21]. We will summarize and describe each identified study's characteristics (eg, author name, study location, and year of publication), as well as the pedagogical and theoretical or conceptual approach used in the design of the MOOC, the learning activities, content, and resources adopted and any participant evaluation of materials used in MOOCs. We will then report the output with an emphasis on describing how the findings relate to the subquestions guiding the scoping review before discussing the implications for pedagogical practice and instructional design of MOOCs targeting prospective postgraduate students in the health sciences.

Consulting Relevant Stakeholders

The sixth stage of the scoping review process is an optional consultation stage [20]. We agree with other researchers who argue that consultation could be useful for knowledge translation [23,24]. We will consider inviting relevant stakeholders, such as international PhD students from LMICs and experts in online, computer-mediated pedagogies, to advice on how to provide appropriate, useable learning resources, and how learning activities or material identified can be used to underpin inclusive, collaborative learning processes among students with diverse backgrounds in a potential revision of the MOOC *How To Write a PhD Proposal.*

To disseminate findings, we seek to publish the scoping review in an international peer-reviewed journal with a scope that includes the use of collaborative pedagogies in computer-mediated and online learning environments. We also aim to disseminate the findings to professionals and other colleagues in postgraduate studies to potentially inspire improved instructional designs of MOOCs.

Results

The scoping review is currently ongoing. As of March 2022, we have completed an initial data search and screened the title and abstract of all references. However, as the initial search captured a large bout of irrelevant published studies beyond the field of study, we decided to revise the search string across all databases in a second literature search. We aim to start analyzing the data in June 2022 and expect to complete the scoping review by February 2023. The proposed scoping review will inform a

potential revision of the MOOC *How To Write A PhD Proposal*. The MOOC is currently delivered on the FutureLearn platform by colleagues from the University of Oslo. The MOOC is funded by the University in Oslo and the NORPART: EXCEL SMART program (2016/10213).

Discussion

We have developed a scoping review protocol aimed at investigating the pedagogical approaches used, and the type of learning activities, content, and resources used to foster social interaction and collaboration when designing MOOCs at postgraduate level in the health sciences.

The findings of the proposed scoping review may have direct implications for academic staff and professionals working with the instructional design or pedagogical practices of MOOCs or in other online, collaborative courses. First, it could directly influence the way key learning activities and tasks are structured or designed in cMOOCs or blended-learning MOOCs. As the proposed scoping review can inform a potential revision of the MOOC in PhD proposal writing, where the first runs had a wide range of participants from both high-income countries and LMICs worldwide, identifying how social or collaborative learning activities and resources can be adjusted to accommodate the needs of students from LMICs or resource-constrained educational system (eg, internet connectivity issues) can result in a higher completion rate of students enlisting for the course [38]. To this end, it could influence the extent of which participants improve the quality of their PhD proposal writing and thus have social implications for the recruitment of candidates to PhD programs in increasingly internationalized research education programs across the globe. Second, understanding how current learning activities, content, or resources can be modified to underpin inclusive, collaborative learning processes among participants with diverse backgrounds, we could potentially improve course designs and the quality of the individual learning experience in MOOCs using a social learning or blended learning approach [19].

We followed the PRISMA-ScR to inform what we reported throughout this protocol [21]. Very few scoping reviews are reported, and even fewer published [39]. We contend that publishing this protocol can contribute to increased transparency and methodological rigor of the final review and future review studies, as many scoping reviews often lack sufficiently detailed descriptions of search strategies and procedures [30,39]. In accordance with the PRISMA-ScR [21], we have therefore detailed our research strategy, the theoretical position, and how this could influence the specific phases of the review procedure. We have also described our search strategy for both published and gray literature databases in a detailed way. As there is usually no methodological assessment of included studies in scoping reviews, using quality appraisal tools such as the MMAT [36] and the AACODS checklist [37] can further increase the rigor, accuracy of interpretation of data, and synthesis of findings [21,23,27]. Through these measures, the potential for reproducibility increases and allows readers of the proposed scoping review to *fully* engage with and assess the assumptions underpinning the work, as well as the specific steps of the scoping review procedure [21].

However, there are limitations related to the scoping review procedure as described in this protocol. As the research team comprises relatively few members, there is a risk that the literature searches can produce an excessive amount of data, which is unfeasible to process and analyze. To mitigate this, we have recruited a research librarian to compile accurate but comprehensive search strategies. If the body of literature proves unmanageable or the database searches are inaccurate, we will further adjust the search string and continuously assess the scope of our search.

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Conflicts of Interest

None declared.

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Abbreviations

HEI: higher Education Institutes
LMIC: low- and middle-income country
MMAT: Mixed Methods Appraisal Tool
MOOC: Massive Open Online Course
PRISMA-ScR: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Asthma and Technology in Emerging African American Adults (The ATHENA Project): Protocol for a Trial Using the Multiphase Optimization Strategy Framework

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Abstract

Background: Asthma causes substantial morbidity and mortality in the United States, particularly among African American emerging adults (AAEAs; aged 18-30 years), but very few asthma programs have targeted this population. Interventions that provide education and address underlying motivation for managing asthma may be the most effective. However, intensive face-to-face interventions are often difficult to implement in this population.

Objective: The purpose of this study is to develop an effective mobile asthma management intervention to improve control among AAEAs.

Methods: We will assess the ability of multiple technologic components to assist and improve traditional asthma education. The first component is the Motivational Enhancement System for asthma management. It is a mobile 4-session intervention using supported self-regulation and motivational interviewing. Personalized content is based on each participant's activity level, daily experiences, and goals. The second component is supportive accountability. It is administered by asthma nurses using targeted mobile support (Skype/voice calls) to provide education, promote self-efficacy, and overcome barriers through a motivational interviewing–based framework. The third component is SMS text messaging. It provides reminders for asthma education, medication adherence, and physical activity. The fourth component is physical activity tracking. It uses wearable technology to help meet user-defined physical activity goals. Using a multiphase optimization strategy (MOST) framework, we will test intervention components and combinations of components to identify the most effective mobile intervention. The MOST framework is an innovative, and cost- and time-effective framework that uses engineering principles to produce effective behavioral interventions. We will conduct a component selection experiment using a factorial research design to build an intervention that has been optimized for maximum efficacy, using a clinically significant improvement in asthma. Participants (N=180) will be randomized to 1 of 6 intervention arms. Participants will be recruited from multiple sites of the American Lung Association-Airway Clinical Research Centers network and ambulatory care clinics at the Detroit Medical Center. Data collections will occur at baseline, and 3, 6, and 12 months.

Results: At study completion, we will have an empirically supported optimized mobile asthma management intervention to improve asthma control for AAEAs. We hypothesize that postintervention (3, 6, and 12 months), participants with uncontrolled asthma will show a clinically significant improvement in asthma control. We also hypothesize that improvements in asthma

management behaviors (including physical activity), quality of life, symptoms, adherence, and exacerbation (secondary outcomes) will be observed.

Conclusions: AAEAs are disproportionately impacted by asthma, but have been underrepresented in research. Mobile asthma management interventions may help improve asthma control and allow people to live healthier lives. During this project, we will use an innovative strategy to develop an optimized mobile asthma management intervention using the most effective combination of nurse-delivered asthma education, a smartphone app, and text messaging.

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KEYWORDS

African American emerging adults; asthma management; mHealth; mobile health; motivational interviewing; asthma control; physical activity

Introduction

Background

Health disparities are evident in many conditions, including cancer, diabetes, and cardiovascular disease. One condition with a significant inequality in health outcomes is asthma. Recent prevalence rates for asthma in the United States show that 7.9% of the adult population has asthma, and this rate is 10.1% among African Americans or Black people. Unfortunately, severity and disease control disparities are significantly worse than the prevalence rates would suggest. For example, the asthma mortality rates are nearly 3 times higher among non-Hispanic African Americans or Black people than among non-Hispanic Whites (22.7 vs 8.1 per million) [1]. Additionally, hospitalization rates are 4 to 5 times higher among African Americans than among Whites [2,3]. Many factors may contribute to these disparities, including both environmental and underlying genetic influences. Urban areas, which often have a predominance of African American residents, are heavily concentrated with risk factors associated with asthma, such as air pollution [4], cockroaches [5], dust mites [6], poor diet [7], poverty [8], stress [9], and violence [10]. Studies have compared African American patients and White patients, and have found that African American patients visit an asthma specialist less often, receive less asthma education, and use an inhaled corticosteroid for persistent asthma less frequently [8,11-13].

African American Emerging Adults With Asthma

This project will focus on African American emerging adults (AAEAs) between the ages of 18 and 30 years, a developmental period largely neglected in the research literature but known to have some of the worst asthma outcomes along with significant health disparities. While significant research has focused on outcomes in adolescence, most markers of asthma control (mortality, quality of life, and health care utilization) are even worse in emerging adults than in adolescents [14,15]. Part of the reason may be that emerging adulthood represents a period of dramatic change for an individual, with identity exploration and self-focus, increased independence and risk-taking, and decreased parental oversight [16,17]. For the first time, emerging adults are responsible for their own health care, finances, education, and employment. Compounding this problem, many pediatricians stop caring for patients once they turn 18 years. Adult practitioners may not be fully trained or equipped to deal with the unique circumstances of emerging adults transitioning out of adolescence [18] or may rely on the "developmental continuity myth," that is, the fallacy of applying adult treatments to youth, with little alteration or changes to the interventions [19]. Successful interventions to improve health outcomes must be developed to meet emerging adults' distinctive developmental needs.

Literature on interventions to improve asthma management in emerging adults is nearly nonexistent [20-22]. Further, African Americans of all ages are underrepresented in mobile health (mHealth) and eHealth studies [23]. Results of studies with racial/ethnic minority adults suggest that culturally appropriate programs that target specific aspects of asthma management (eg, adherence and physical activity) have largely been successful [24]. Thus, interventions that similarly target AAEAs at the highest risk for poor asthma management and health outcomes may have promise for improving morbidity and mortality rates. Interventions must consider the target group's distinctive cultural and developmental needs and challenges. This project tests a developmentally and culturally appropriate intervention for AAEAs with persistent asthma.

Call for Technology-Based Mobile Interventions

There are multiple barriers to intervention delivery, including buy-in at multiple levels (eg, department and community), personnel turnover, and reproducibility. Emerging adults may also be unlikely to complete intensive in-person interventions [25]. Technology-based interventions cannot replicate important human elements of interventions, but they offer advantages in terms of reach, cost, anonymity, and scalability. While there are over 500 asthma-related apps in the Apple Store and Google Play Store, a review in 2019 found that less than 10 have actually been evaluated in clinical trials [26]. Most of these evaluations were conducted with adolescents, were focused on caregivers, or were implemented in school settings. Attrition in eHealth interventions is also common [27], and very few mHealth interventions have been grounded in behavior change theory. The use of SMS text message reminders can improve self-management in people of all ages with asthma [28,29], though the magnitude of improvement tends to be small. Mobile interventions have rarely examined the integration of remote nursing support with a theory-based program. The synergism of such an approach has potential additive effects that urgently require further exploration. Finally, mHealth interventions can

be designed to address the concerns and barriers faced by racial/ethnic minority groups or those of low socioeconomic status, as the challenges and goals are often different among such populations [26]. The proposed project will utilize an innovative and cost-efficient framework to identify the most effective combination of intervention components to improve asthma control in AAEAs.

Theoretical Model

Nearly every guideline notes that asthma education plays a critical role in disease management [30]. Educational strategies based on behavioral theories of change, such as motivational interviewing (MI), are more likely to be effective than strategies that simply provide information. MI is a collaborative goal-oriented style of communication with particular attention to the language of change. It is designed to strengthen intrinsic motivation for and commitment to a goal by eliciting and exploring the person's own reasons for change within an atmosphere of acceptance and compassion. Research on the mechanisms of effect in MI has concluded that patient "change talk" (ie, statements about their own desire, ability, reasons, or commitment to change) consistently predicts actual behavior change. Several behavior change theories are consistent with MI. First, the Self-Regulation Theory (SRT) has core principles hypothesizing that multiple factors interact to influence behavior. The most influential way in which a person develops expectations and solidifies a behavioral change is through personal experience, which underlies improvement through self-regulation [31]. Zimmerman described self-regulation as a process of the following 3 phases: self-observation, self-judgment, and self-reaction [32], and Zimmerman and Clark adapted these subprocesses for asthma [33]. Through the self-regulatory process, the person is able to observe and learn from experience and determine ways for changing behavior (Figure 1). Second, the Information-Motivation-Behavioral Skills (IMB) model [34] posits that behavior change results from the joint function of the following 3 components: accurate information about risk behaviors (eg, not managing asthma) or their replacement behaviors (eg, benefits of following an asthma management regimen), the motivation to change behavior, and the perceived behavioral skills necessary to perform the behavior (eg, self-efficacy) (Figure 2). A powerful attribute of the IMB model is its ability to improve the self-efficacy needed for behavior change. For the intervention, we have combined the most powerful components of these complementary theories to build an asthma management intervention that not only targets asthma education, but also addresses underlying motivation and provides social support for change.

Figure 1. Self-regulation processes in disease prevention and management.

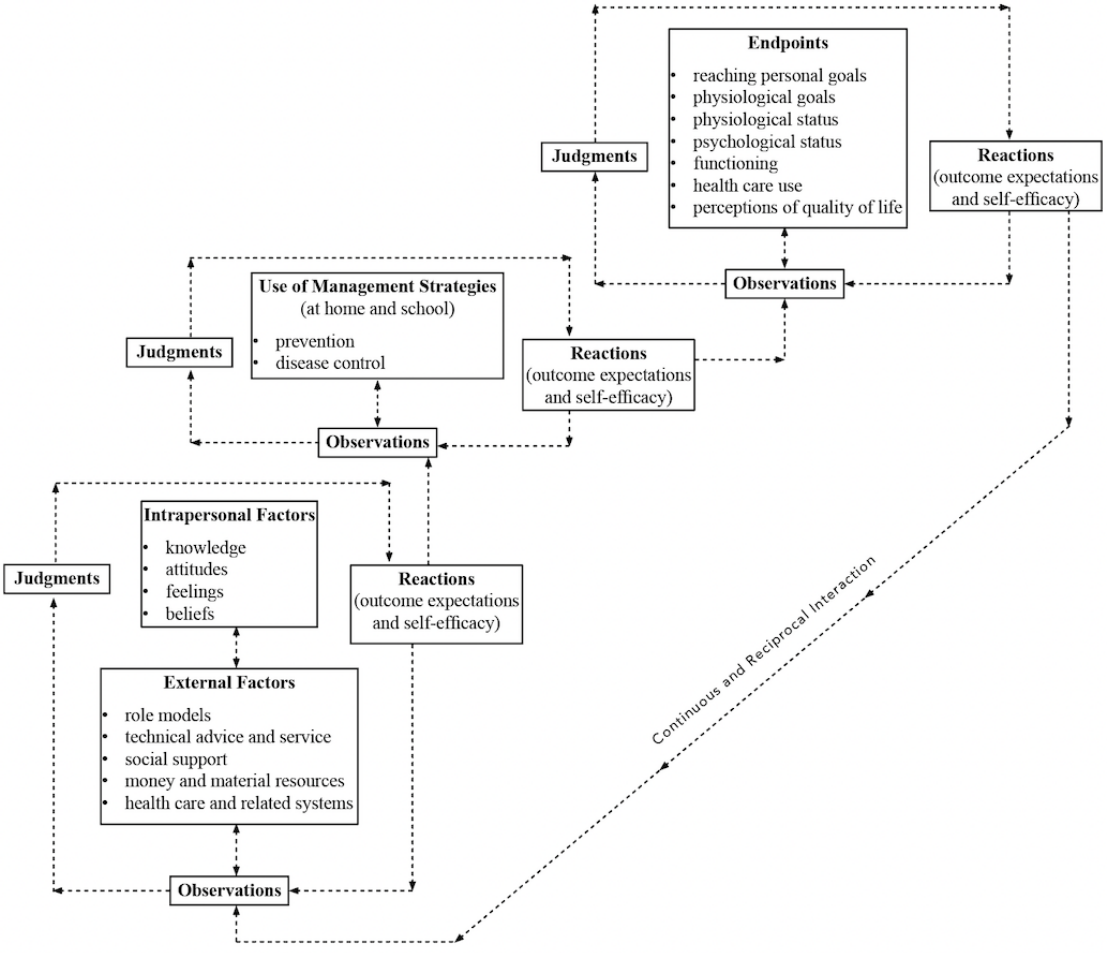
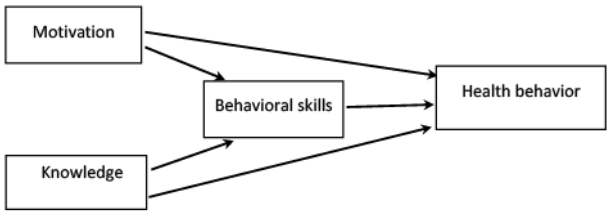


Figure 2. Information-Motivation-Behavioral Skills model.



Study Aims

The purpose of this study is to develop an effective mHealth intervention to improve asthma management and asthma control among AAEAs. We have developed and tested technology-based theoretically grounded asthma self-management interventions for AAEAs that will be refined and evaluated as components of a resulting mobile asthma management intervention. These intervention components are based on the SRT or IMB model, and utilize MI. We will evaluate 4 intervention components for synergistic effects. The first component is the Motivational Enhancement System (MES) for asthma management. The MES is a mobile 4-session MI intervention using supported self-regulation to enhance motivation for asthma management and asthma knowledge. Personalized content is chosen by a computer algorithm, and is based on each participant's self-regulation stage, activity level, daily experiences, and goals. The second component is supportive accountability (SA). SA is administered by asthma nurses using targeted mobile support (Skype/voice calls) to provide education, promote self-efficacy, and overcome barriers through an MI-based framework. The third component is SMS text messaging (TXT). It provides asthma management education. The fourth component is physical activity tracking (PAT). PAT uses wearable technology (eg, a smart watch) for meeting user-defined activity goals as part of the asthma management regimen.

Participants will be recruited from multiple sites of the American Lung Association-Airway Clinical Research Centers network and clinics at Wayne State University/Detroit Medical Center and the University of Michigan. Participants (N=180) with uncontrolled persistent asthma will be randomized to 1 of 6 intervention arms consisting of combinations of the 4 components through a multiphase optimization strategy (MOST) design. The MOST design is an innovative, and cost- and time-effective experimental design that utilizes engineering principles to test behavioral interventions. The MOST design uses an optimization criterion to make decisions and refine the efficacy of each of the intervention components. We will adopt clinically significant improvements in asthma control (defined as a change of ≥3 on the Asthma Control Test [ACT]) as an optimization criterion in a component selection experiment using a randomized factorial design. This experiment is equivalent to conducting multiple pilot randomized clinical trials to evaluate the efficacy of each component, yet uses only a fraction of the sample size, resources, and time. At the completion of this study, we will have developed an empirically supported mobile asthma management intervention to improve asthma control for high-risk AAEAs.

Methods

Study Participants and Setting

Phase 2 consists of a clinical trial study. The study will include 180 AAEAs (30 per arm; N=150 + 20% attrition) aged 18-30 years with persistent asthma that is not fully controlled (defined as a score of less than 19 on the ACT) [35]. We have intentionally chosen uncontrolled asthma patients as the program is designed to help take control of their asthma, and these patients would be the most motivated to use such an intervention. Participants must also own or have access to a cellular phone for the duration of the study and have a primary care physician. Recent data from the Pew Research Center demonstrate that 98% of Black individuals currently own a cellular phone, and that 96% of those aged 18-29 years own a smartphone [36]. To encourage participation, we will pay the cellular bill during the 8-week intervention period for all participants, a strategy that we and others have found to be extremely effective in this population. This will be in addition to the participation incentives. The exclusion criteria will be any other significant cardiopulmonary disease (including chronic obstructive pulmonary disease), a greater than 20 pack-year smoking history (as this level has been associated with the development of chronic obstructive pulmonary disease) [37], developmental delay or mental illness such that participation in the program would not be possible, and pregnancy. Women who become pregnant during the course of the study will be allowed to participate with written approval from their physician. Finally, as PAT will be part of the intervention, any subject who is unable to do mild physical activity for any health reason (including asthma) will be excluded. The ability to participate in mild physical activity will be verified by each participant's primary care provider.

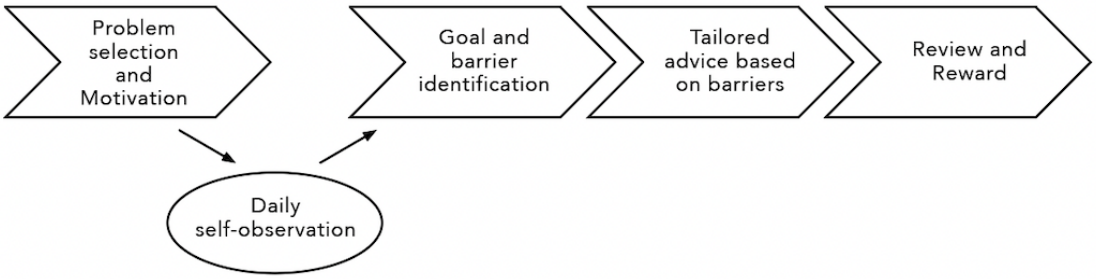
Participants will be recruited through clinical and community locations. Clinical locations will include the American Lung Association-Airway Clinical Research Centers network, as well as clinics at the University of Michigan, Wayne State University, and Detroit Medical Center. Community locations will utilize online recruitment primarily through social media, using procedures we have developed in previous work [38,39]. All components of the trial (including recruitment, signed informed consent, and intervention education components) will be done remotely.

Proposed Intervention Components

MES

The MES is a web-based mobile asthma management intervention delivered via the Computerized Intervention Authoring Software (CIAS 3.0) platform [40] on participants' personal mobile devices. Despite being an automated mobile program, the MES is *tailored* for each participant in several ways. First, at baseline, participants will be classified according to their Asthma Self-Regulatory Development stage [41], which will guide behavioral content and number of sessions that each receives. Second, the MES is an interactive program that is individualized based on MI principles and participant-selected barriers/goals. Third, participants receive personalized feedback based on their responses to a daily diary completed between sessions 1 and 2, which prompts for barriers and facilitators to daily asthma management and control. Fourth, delivered content is based on a computer algorithm that incorporates the stage of asthma self-regulation to determine the number and frequency of sessions. Sessions are provided by an animated character (avatar) developed via focus groups with African Americans. Significant efforts have been made to ensure that the avatar delivers the intervention in a way that engages AAEAs with empathy, optimism, and autonomy support. The MES focuses on asthma management behaviors with feedback on asthma symptoms, physical activity, adherence, and tailored education. The avatar evokes both importance and confidence (key components of motivation) with MI strategies, such as identification of the benefits of behavior change, affirmations to reinforce change talk and boost confidence, and identification of personal strengths and resources. The avatar reflects (summarizes what the participant is saying to convey understanding) without judgment and provides statements to emphasize autonomy. Participants will follow a 4-step sequence of problem-solving based on the principles of the social cognitive theory, particularly self-regulation, and MI. This will include problem selection, self-observation with an online diary, goal selection, barrier selection, and reward selection, as participants progress through the 4 sessions (Figure 3).

Figure 3. Flow of motivational enhancement system and supportive accountability intervention components.



SA

SA is an asthma management intervention delivered by asthma nurses trained in targeted MI skills (eg, open-ended questions around change talk and affirmations) via participants' personal mobile devices (eg, Skype, FaceTime, voice calls, and SMS text messages). The theory underlying SA is that education and behavior change are most impactful when delivered by a knowledgeable yet supportive authority figure (ie, nurse) [42]. SA and the MES will be matched for number, timing, and focus of sessions. Sessions include promoting motivation for asthma management, education, feedback from participant reports of symptoms and management behaviors, enhancing self-efficacy, and goal setting. A total of 4 discrete sessions, as well as an asthma online diary, will be used in the SA intervention. SA sessions will also provide real-time exploration of barriers and problem-solving around asthma management, and will allow greater flexibility than the MES because they are delivered by a nurse interventionist versus an automated program. For instance, participants can choose topics beyond those on the MES list of most commonly chosen problems. SA calls include scripted components to check-in on asthma management activities but are otherwise flexible to allow focus on tailored barriers and issues a participant may have surrounding asthma management and control.

Asthma nurses will be provided with training in tailored MI. The following 3 provider communication behaviors have been found to be the strongest predictors of patient change talk: emphasizing patients' autonomy, open-ended questions to elicit change talk, and reflections of change talk [43-45]. For this study, it is not feasible to train nurses to full MI competency, so our team has developed an approach to provide training in fundamental MI skills linked to behavior change [43]. Training will be provided by trainers certified by the Motivational Interviewing Network of Trainers and will include an initial 2-day workshop, followed by fidelity monitoring and boosters. MI fidelity will be monitored through audio recordings from SA sessions and rated using the MI Coach Rating Scale (MI-CRS) [46]. The MI-CRS is a 12-item measure of MI competence. Nurses will be trained in the interpretation of data from study-provided smart watches and will use this to encourage activity and asthma management.

TXT

SMS text messages will target asthma knowledge. These messages will be sent via CIAS 3.0 to participants' personal mobile devices with facts about asthma management, links to educational web content, and videos providing information about living with asthma. A library of asthma education text messages developed during previous work will be refined and expanded using information from the CDC "Learn how to Control your Asthma" website [47]. Information covered

includes "What is asthma," "What is an asthma attack," "What causes an asthma attack," "How is asthma treated," "Asthma and weather," "Using an inhaler," "Using a spacer," and "Asthma action plans." Messages will be sent twice a week for 4 weeks and then once a week for 4 weeks. SMS text messages will be formatted to fit a smart watch (see below) so that participants can use the study-provided device.

PAT

All participants, including those in the control arm, will be provided a smart watch in the form of an Apple Watch or Android watch. This PAT device will allow participants to accurately track exercise and total steps each day [48]. The US 2018 Physical Activity Guidelines Advisory Committee Scientific Report found "moderate" to "strong" evidence that mobile phones and wearable devices increase physical activity [49]. Through PAT, users will be able to set daily goals and attain or improve motivation to continue asthma management. For individuals randomized to groups that also include the MES or SA, those programs will incorporate PAT data that are remotely transmitted, to facilitate asthma management motivation. In formative work, AAEAs were enthusiastic regarding interventions that provided users a smart watch, and stated they were much more likely to continue in a trial that did so.

Intervention Component Refinement

The MES, SA, and SMS components have been developed in previous work with different patient populations and behavioral targets. The current protocol includes 2 phases. During Phase 1 of the project, all 3 components will be refined and beta-tested for use with AAEAs having uncontrolled asthma. Minor adjustments will be required as we will now be integrating components both alone and in combination. Additionally, component refinement will be achieved with significant input from relevant stakeholders. Stakeholders include AAEAs with asthma, asthma nurses, asthma educators, primary care physicians, asthma specialty physicians, and computer specialists. All content has been developed through multi-step formative work, but it is important to continue to refresh and update content (eg, changing asthma guidelines and social phenomenon). For the primary stakeholder (AAEAs with asthma), 3 focus groups (4-6 individuals per group) will be held; the specifics of each component to be discussed are described below. Finally, prior to evaluation in the trial, beta-testing with a group of 10 AAEAs with asthma will be performed for each component arm to ensure that combinations are acceptable and well-integrated. Beta-testers will be asked to use assigned components, followed by an interview to obtain feedback on content, delivery, and technological issues.

Qualitative Data Analysis

We will utilize a systematic, yet flexible, approach to thematic analysis to maintain rigor within the study timeline. Data will be managed and coded using NVivo 12. Two members of the research team will utilize the Framework Method, now used widely in health research [44-46,49-52]. Its defining feature is the matrix output, providing a structure to systematically reduce the data for analysis on various levels. After transcription, analysis will proceed through several stages: (1) familiarization with the session; (2) thematic coding; (3) developing a working analytical framework; (4) applying the framework; (5) charting data into the framework matrix; and (6) interpreting the data.

Study Trial Design

This project will use the MOST [53-55] framework to optimize a mobile intervention to enhance the asthma management behaviors of AAEAs. The MOST design allows the evaluation of not only efficacy, but also efficiency, economy, scalability, and sustainability [56]. We will first refine the intervention components (MES, SA, PAT, and TXT) based on input from key stakeholders, including asthma nurses and AAEAs with asthma. We will then conduct a component selection experiment using a factorial research design to build an intervention that has been optimized for maximum efficacy. We will use a clinically significant improvement in asthma control (a change of ≥3 on the ACT [35]) as the criterion for determining which components should be kept in the optimized intervention. During the study, participants, their physicians, and any members of the study team who are adjudicators of outcomes will be unaware of study group assignment to the extent possible in a behavioral trial.

This study will use a 6-arm incomplete factorial design for the component selection experiment (Table 1). A full factorial design will not be used as some of the experimental combinations cannot be present simultaneously (eg, MES and SA are mHealth and involve human delivery of the same intervention content, and therefore logically cannot be combined), and PAT will be provided to all participants. Byar et al [57] described such incomplete designs, and in particular, we are employing "Design 3," which is a "$2^3 - Y_{AB} - Y_{ABC}$" design. This design matches with our experimental combination as MES (A) and SA (B) components cannot occur together. Table 1 shows the incomplete factorial design given the possible combinations of the 4 components [55]. As the full factorial design is not feasible for the current setup, we also considered a 2^{3-1} fractional factorial design with 3 factors but with 4 (2^{3-1}) treatment conditions, allowing aliasing of the highest-level interaction (ie, each main effect will be confounded with a 2-factor interaction). However, our design with 6 components is a superset of that 2^{3-1} fractional factorial design and will result in better evaluation of treatment combinations than any fractional factorial (see the study by Byar et al [57]). This design preserves much of the full factorial structure and provides more reasonable results than a fractional factorial design [58]. This design also allows evaluation of the main effect of each component and exploration of interaction effects when components are combined, though more assumptions are needed as a full factorial (=2^3) is not present. One assumption is a "saturated design" when the combination missing (AB and ABC) is assumed to be 0 or have no effect. The component selection experiment is powered for the main effects and will include 180 participants (or 30 participants per arm).

Table 1. Intervention conditions.

Experimental condition	Motivational Enhancement System	SMS text messaging	Supportive accountability	Usual care	Physical activity tracking
1	Yes	No	No	No	Yes
2	No	Yes	No	No	Yes
3	No	No	Yes	No	Yes
4	Yes	Yes	No	No	Yes
5	No	Yes	Yes	No	Yes
6	No	No	No	Yes	Yes

Study Procedures

All data collection and intervention activities will take place remotely. Following enrollment, research assistants will contact participants for consent and onboarding/orientation. Participants will receive US $25 per assessment for a total of US $100 and keep the Apple or Android watch. Participants will receive US $50 per month during the 2-month intervention period to offset the cost of their cell phone bill. To enhance engagement, this incentive will only be offered if participants remain above a determined threshold of response (eg, answer 80% of SA calls, text messages, etc), to be determined by key stakeholders during focus groups [59]. Data collection and most intervention activities will be conducted using CIAS 3.0. CIAS 3.0 is an HTML5 mobile web app with a responsive design capable of being deployed on any web browser accessed via any device (eg, Apple or Android smartphones) of any size (ie, auto reformat for optimal viewing on any size screen). This mobile version has an enhanced feature set, including improved voice quality for narrated content and appearance. Data collection sessions will take less than 30 minutes to complete. Participants will be randomized following baseline. Because the assessment is computer administered, there is no data collection staff per se for written measures.

Randomization

Participants will be randomized to 1 of 6 study arms following baseline. Randomization will be stratified by sex as we expect 65%-70% of subjects to be female (given the demographics of asthma among AAEAs). We will randomize using permuted blocks with sex as a stratification variable. Permuted blocks have the advantage of ensuring a balance between treatment arms for important prognostic variables without unmasking the next treatment allocation [60]. The randomization program/code will be developed and maintained centrally by a biostatistician.

Measurement

Data collection will occur at baseline, 3 months (postintervention), 6 months, and 12 months. At baseline, demographic information, asthma-specific information, and psychosocial information will be collected. The primary outcome will be improvement in asthma control as assessed by the ACT [35,61]. The mediators of asthma control will be based on the evaluation of IMB and SRT constructs, including asthma knowledge, attitudes, motivation, self-management behaviors, and self-efficacy.

Although we have feasibility data for the individual components, we will now obtain data for component combinations. Questionnaires and qualitative methodology will be used to determine recruitment and retention, adherence to the program, suitability and variability of outcome measures used, application and fidelity of the program, and demand/acceptability of the program for patients and professionals [62].

Statistical Analysis

We will initially characterize the data heterogeneity and frequency distributions of asthma control, the primary outcome, and all secondary outcomes (asthma management and IMB/SRT constructs). We will check for out-of-range values, outliers, and abnormal values using graphical methods and create descriptive summaries to ensure that all values are within expected ranges. Unexpected findings will prompt checking of raw data for accuracy of data entry and recording. We will analyze the effect of the intervention components on the longitudinal measures of asthma control (ACT) using a mixed effects linear model for repeated measures analysis of variance (ANOVA) of a factorial design. This model will include a fixed effects indicator for each intervention component (SA, MES, TXT, and PAT) and time, along with all interactions with time. Random intercepts will be used to account for the longitudinal nature of the data. Before evaluating which components contribute to a potential change in the ACT score, we will use the model to compare the treatment with all 3 components and the control condition to determine whether the complete intervention is efficacious. If this statistical test is significant, we will identify those components that result in a significant change in the ACT score by examining the interactions between the main effects and time using the strategy advocated by Collins et al [53], which begins with the simplest effects and only adds higher-order interactions if needed. We will use a P value of <.05 for the test of total effect (difference between the treatment with all 3 components and the control treatment) and .1 to identify which components contribute to the total effect. We will use a higher threshold for the component selection test because we want to reduce the likelihood of not selecting a component that is contributing to the total effect. Secondary outcomes will be analyzed using a similar approach, but they are not powered. If significant baseline group imbalance is detected for any variable and its correlation with the outcome is 0.30, that variable will be included as a covariate in the inferential analyses. Dropouts and completers will also be compared in terms of baseline variables.

Institutional Review Board Approval

The research protocol and study materials were reviewed and approved by the Wayne State University Social, Behavioral, and Education Review Board on September 1, 2021. Wayne State University (WSU) operates its Human Research Protection Program under a Federal wide Assurance (FWA) on file with the Office for Human Research Protection with identification number: FWA 00002460. The Social, Behavioral, Education board (B3) is IRB00000327.

Results

Recruitment for intervention refinement via focus groups and beta-testing began in January 2022. Focus groups will be completed in March and April 2022. Recruitment for the trial is scheduled to begin in June 2022. The study results will be available within 12 months after the final data collection date (expected 2025). Results of Phase 1, including qualitative analyses from focus groups and the process of adaptation, will be available in late 2022. The findings will be disseminated to stakeholders using various methods, including peer-reviewed journals, academic conferences, and other communication modalities.

Discussion

Overview

Asthma causes substantial morbidity and mortality in the United States, particularly among AAEAs, but very few asthma programs have targeted this population and there are few interventions specifically designed to improve asthma control in this group. The study aims to significantly advance behavioral interventions for AAEAs with uncontrolled asthma. Interventions that provide education and address underlying motivation for managing asthma may be the most effective. However, intensive face-to-face interventions are often difficult to implement, especially among emerging adults. The purpose of this study is to develop an effective mobile asthma management intervention to improve asthma control among AAEAs. For this study, physical activity will be included as an important aspect of asthma management. The project utilizes the MOST framework to identify the best possible intervention component or combination of components to help AAEAs improve asthma control and, subsequently, lead healthier lives. At the completion of the study, we will have an empirically supported optimized mobile asthma management intervention to improve asthma control for AAEAs. Because the intervention is mobile and centralized, it has high potential for future scalability and implementation in clinical and community settings. Additionally, this project will enhance our understanding of barriers to and facilitators of asthma management and control among AAEAs, as well as the role of physical activity in managing asthma.

Limitations

Although this study will lead to an optimized intervention for an underserved and at-risk population, there are potential limitations. Differential loss to follow-up is a threat to internal validity to assess the effect of components. Possible barriers to completion are high rates of no-shows at clinic visits and refusal to participate. Recruitment procedures and strategies have been the primary focus throughout our work because AAEAs with asthma are difficult to recruit. We have anticipated recruitment challenges and have developed community and online recruitment sources (social media). Another possible limitation is retaining participants for 12 months. Our research centers have an established history of working with at-risk urban populations and strong retention rates [38], and have developed various techniques to sustain engagement, including reminder letters, texts, and phone calls. Threats to the internal validity of the study may arise without sufficient attention to quality assurance of data collection and intervention delivery. Possible technological difficulties were minimal and remediated in previous work, resulting in protocols for technical support. Feasibility assessments and adaptive flexibility will be hallmarks of the protocol.

Conclusions

This study will contribute to the existing literature on AAEAs with asthma; moreover, if successful, the project will result in an optimized intervention package specifically tailored for AAEAs with uncontrolled asthma to effectively improve asthma control. This is critical because emerging adulthood represents a unique period of development with challenges that may impact asthma management and asthma control; moreover, few studies and interventions have focused on improving asthma control among AAEAs. Planned next steps may include a large-scale multi-site effectiveness randomized controlled trial of the resulting optimized intervention package.

Acknowledgments

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Authors' Contributions

AB and KKM wrote the manuscript and designed the study protocol. AIC, WGS, and SG reviewed and edited the study protocol. AIC, AJT, WGS, and AH edited the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

National Institutes of Health peer-review report.
[PDF File (Adobe PDF File), 140 KB - resprot_v11i5e37946_app1.pdf]

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Abbreviations

AAEA: African American emerging adult
ACT: Asthma Control Test
CIAS: Computerized Intervention Authoring Software
CRS: Coach Rating Scale

IMB: Information-Motivation-Behavioral Skills
MES: Motivational Enhancement System
mHealth: mobile health
MI: motivational interviewing
MOST: multiphase optimization strategy
PAT: physical activity tracking
SA: supportive accountability
SRT: Self-Regulation Theory
TXT: SMS text messaging

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Protocol

Evaluation of a Circadian Rhythm and Sleep-Focused Mobile Health Intervention for the Prevention of Accelerated Summer Weight Gain Among Elementary School–Age Children: Protocol for a Randomized Controlled Feasibility Study

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Abstract

Background: The i♥rhythm project is a mobile health adaptation of interpersonal and social rhythm therapy designed to promote healthy sleep and behavioral rhythms among 5-8-year olds during summer for the prevention of accelerated summer weight gain.

Objective: This pilot study will examine the feasibility, acceptability, and preliminary efficacy of the i♥rhythm intervention. This will ensure that the research protocol and procedures work as desired and are acceptable to families in preparation for the fully powered randomized controlled trial. The proposed study will examine the willingness of participants to participate in the intervention and determine whether modifications to the intervention, procedures, and measures are needed before conducting a fully powered study. We will assess our ability to (1) recruit, consent, and retain participants; (2) deliver the intervention; (3) implement the study and assessment procedures; (4) assess the reliability of the proposed measures; and (5) assess the acceptability of the intervention and assessment protocol.

Methods: This study will employ a single-blinded 2-group randomized control design (treatment and no-treatment control) with randomization occurring after baseline (Time 0) and 3 additional evaluation periods (postintervention [Time 1], and 9 months [Time 2] and 12 months after intervention [Time 3]). A sample of 40 parent-child dyads will be recruited.

Results: This study was approved by the institutional review board of Baylor College of Medicine (H-47369). Recruitment began in March 2021. As of March 2022, data collection and recruitment are ongoing.

Conclusions: This study will address the role of sleep and circadian rhythms in the prevention of accelerated summer weight gain and assess the intervention's effects on the long-term prevention of child obesity.

Trial Registration: ClinicalTrials.gov NCT04445740; https://clinicaltrials.gov/ct2/show/NCT04445740.

International Registered Report Identifier (IRRID): DERR1-10.2196/37002

(JMIR Res Protoc 2022;11(5):e37002) doi:10.2196/37002

KEYWORDS

summer; circadian rhythms; sleep; child obesity; elementary school

Introduction

Accelerated summer weight gain has been shown to contribute to increasing rates of overweight and obesity during elementary school [1,2]. However, school-summer differences in diet, physical activity, and sedentary behavior have not been associated with differences in the rate of BMI change during the school year and summer [3]. While summertime interventions targeting children's physical activity during summer have been demonstrated to increase physical activity levels, their impact on children's BMI outcomes remains less clear [4]. These findings underscore the need to consider novel determinants of accelerated summer weight gain in the designs of interventions [5].

The transition from the school year to summer represents times during which students experience changes in their behavioral rhythms and routines [6]. Circadian rhythm misalignment has been implicated as a risk factor in obesity onset [7-9] and may be part of this seasonal/school-year variation. Specifically, shifts in the daily behavioral rhythms of sleep [10-13] are associated with increased adiposity, mediated through subsequent desynchronization between the central circadian clock in the suprachiasmatic nucleus and peripheral clocks [7,9,14]. School provides a natural structure for families, requiring children to follow a relatively consistent routine, promoting consistent sleep-wake patterns, mealtimes, and physical activity patterns. During out-of-school times such as summer vacation, bedtime is often later [15-17]. Later sleep timing may contribute to shortened sleep duration among younger elementary school-age children who fail to compensate with a delayed wake time [15]. Both shortened and more variable sleep duration have been associated with increased obesity risk in elementary-age children [10,12,18,19].

Differences in children's sleep, physical activity, and light exposure during the school year and summer were related to children going to bed 1.5 hours later in summer compared with the school year [17]. Having a later sleep midpoint during summer predicted greater increases in BMI during summer, but was not associated with a change in BMI during the school year. Additionally, greater levels of outdoor light exposure during the school year predicted smaller increases in BMI during the school year. Interestingly, sleep duration, day-to-day variability in the midpoint between sleep onset and offset, physical activity levels, and sedentary behavior were not associated with a change in BMI during the school year or summer [17]. However, the importance of sleep timing and light exposure to changes in children's BMI during the school year and summer suggests the potential importance of circadian rhythm–related behaviors, such as sleep timing and light exposure, for promoting a healthy weight status in children. To our knowledge, there is a lack of interventions designed to promote healthy sleep and behavioral rhythms among children during summer.

Interpersonal and social rhythm therapy (IPSRT) is an evidence-based treatment for bipolar disorder that promotes regularity of behavioral rhythms, such as sleep-wake cycles, meal times, and physical activity, to prevent desynchronization of endogenous circadian rhythms that precede depressive and manic episodes [20]. Behavioral rhythms are self-monitored, and behavioral strategies are used to increase the consistency of routines [20-22]. IPSRT is based on social zeitgeber theory [23], which posits that work schedules, family life, and community act as cues affecting circadian entrainment. These influences can be characterized as social demands, which influence circadian entrainment or the synchronization of circadian rhythms through "gating" exposure to the light-dark cycle and influencing the timing of behavioral rhythms [24]. It is hypothesized that a change in social demands such as the transition from the school year to the summer environment may lead to a change in behavioral rhythms [25,26], such as the timing of sleep, meals, and evening screen time, resulting in a change in exposure to morning and evening light as well as increased day-to-day variability. These changes in exposure may result in circadian misalignment, thus predisposing individuals to obesity [25-27]. Adapting IPSRT to promote healthy sleep and behavioral rhythms in children may offer promise as a method to prevent accelerated summer weight gain among children during summer.

The i♥rhythm project is an adaptation of IPSRT. It aims to promote healthy sleep habits and stable behavioral rhythms during summer for the prevention of obesity in young elementary school-age children. The intervention is designed to be delivered via mobile health (mHealth) technologies to better reach parents during summer. Parents receive information about the importance of healthy sleep and consistent behavioral rhythms and are guided through a series of steps to develop plans to support their child's healthy sleep habits and stable behavioral rhythms during summer. This paper describes the research design, methods, and data analysis plan for an ongoing randomized controlled trial designed to evaluate the feasibility, acceptability, and preliminary efficacy of the i♥rhythm project to prevent accelerated summer weight gain. It is hypothesized that a priori feasibility criteria will be met and the intervention and assessment protocol will be found to be acceptable by participants (feasibility and acceptability criteria are outlined in detail in the "Methods" section). As this is a feasibility study, it is not powered to detect differences between groups; however, we anticipate that participants in the treatment condition will have an earlier circadian phase as measured by dim light melatonin onset (DLMO) and changes in BMI will be in the expected direction. Specifically, after intervention, participants in the i♥rhythm project will demonstrate earlier DLMOs and smaller increases in BMI compared with participants in the control condition.

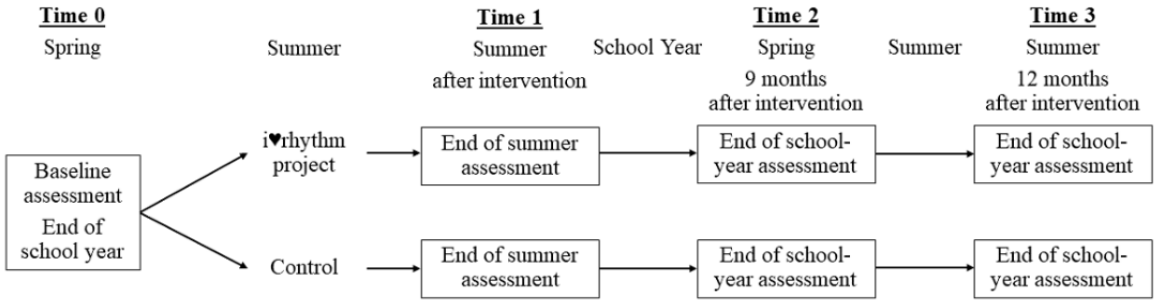
Methods

Study Design

Figure 1 illustrates the study timeline. We will employ a single-blind 2-group randomized control design (treatment and control) with randomization occurring after baseline in the spring/end of the school year (Time 0) and 3 postintervention evaluation periods: immediately after intervention (end of summer; Time 1), 9 months after intervention (spring; Time 2), and 12 months after intervention (summer; Time 3). Because the primary objective of the i♥rhythm project is to prevent

children from beginning a trajectory toward overweight/obesity in elementary school, we will explore the impact of the intervention on change in BMI during the following summer (Times 2-3), identifying whether a maintenance intervention is needed. Following the intervention (Time 1) and final data assessment (Time 3), qualitative interviews will explore the acceptability of the intervention, barriers, facilitators, difficulties with study procedures, maintenance of improvements, and self-efficacy to maintain improvements.

Figure 1. Study timeline.



Participants

The i♥rhythm project is intended for children between the ages of 5 and 8 and their parents. This age group was selected because by using group-based trajectory modeling, we identified that about 19% of children began a trajectory toward overweight/obesity beginning the summer after kindergarten and the summer after second grade [28]. To be eligible for participation parent-child dyads must meet the following criteria: (1) index child must be between 5 and 8 years old and enrolled in kindergarten, first, or second grades; (2) index child must have a BMI >50th percentile (BMI>50th percentile in elementary school is associated with greater risk of transitioning to an unhealthy weight status or obesity at age 12 [29]); (3) parent identifies as a daily user of social media and willing to engage in a social media intervention on Facebook; (4) parent owns a smartphone; (5) parent is comfortable participating in the intervention and responding to questionnaires in English; (6) families must live within the Greater Houston area and be willing to attend 4 in-person assessment visits at the Children's Nutrition Research Center (CNRC). Exclusion criteria include parent report that the index child (1) has been diagnosed with a chronic medical condition that influences sleep, eating behaviors, weight status, or circadian rhythms; (2) is being treated with a medication or supplement known to affect sleep, such as melatonin or stimulants; (3) has been retained 2 or more grades for academic reasons or has intellectual difficulties that would influence their ability to complete questionnaires or participate in interviews; (4) has participated in an obesity prevention or obesity treatment program in the last 6 months.

Sample Size

Sample size recommendations for pilot studies vary, with some recommending 30 per group and others suggesting a few as 12 per group [30-33]. Our intention at the outset of the trial was to recruit 30 parent-child dyads per group. To account for an attrition rate of up to 20% [34,35] we aimed to recruit 36 parent-child dyads per group. The trial was intended to begin in the Spring of 2020, but due to the COVID-19 pandemic, the start was delayed by 1 year. Because of a delay in the trial start date, our recruitment goals were amended. Given the shortened study timeline, the new recruitment goal was to recruit a sample size of 16 parent-child dyads per group. Accounting for an attrition rate of up to 20%, this established a new recruitment target of 20 parent-child dyads per group (40 total parent-child dyads).

Procedures

Recruitment

Recruitment began in March 2021. Because this study will examine the feasibility of a summertime intervention, parent-child dyads will be recruited only in the spring school semester, according to the Houston Independent School District Academic Calendar (approximately February through May). Participants will be recruited through a volunteer database and Facebook advertisements targeting families in the local Houston, Texas area. Data collection will not occur within 1 week following the transition to Daylight Saving Time [36].

Eligibility Assessment and Consent

Interested families will complete an online eligibility questionnaire that is accessed either through an email or a Facebook advertisement. To minimize in-person visits during the pandemic, families that completed the online questionnaire and were eligible will attend a virtual screening visit using Zoom to confirm their eligibility. Before the virtual visit, families will be provided a copy of the consent form and a video with instructions for collecting height and weight in the home [37]. If a digital scale or a measuring tape/ruler is not available in the home, one will be mailed to families. On the Zoom call, informed consent will be obtained, and parents will complete the at-home assessment of height and weight to verify that the child's BMI is >50th percentile. Eligible families will then be scheduled for a baseline assessment at the laboratory that will take place between April and the commencement of the summer break from school. Time 1 assessment will begin following the conclusion of the 5-week intervention with the goal of completing all assessments during the remaining summer break before returning to school. Time 2 and 3 assessments will occur 9 months (end of the school year) and 12 months (end of summer) after completion of the intervention, respectively (Figure 1 and Table 1).

Table 1. Measurement timeline.

	Time 0	Intervention	Time 1	Time 2	Time 3
Primary outcomes					
Recruitment goals	✓	✓			
Intervention fidelity		✓			
Intervention adherence		✓			
Acceptability of assessments			✓		✓
Treatment acceptability			✓		
Retention		✓	✓	✓	✓
BMI	✓		✓	✓	✓
Dim light melatonin onset	✓		✓	✓	✓
Secondary outcomes					
Sleep as assessed by actigraphy	✓		✓	✓	✓
Body composition	✓		✓	✓	✓
Dietary assessment	✓		✓	✓	✓
Physical activity/inactivity	✓		✓	✓	✓
Covariates					
Parent-child demographics	✓				
General and sleep-related parenting practices	✓		✓	✓	✓
Perceived stress (parent)	✓		✓	✓	✓
Social support (parent)	✓		✓	✓	✓
Child care during summer	✓		✓	✓	✓

Randomization

Following the baseline visit, parent-child dyads will be randomized to conditions (experimental or control). Because sleep duration has been shown to differ by sex [38,39], obesity status [10,40], and socioeconomic status (SES) [41], participants will be randomized to condition using a stratified permuted blocks procedure programmed by our biostatistician (SM) in SAS version 9.4 (SAS Institute Inc.). Participants will be identified as being male/female (according to sex at birth), healthy weight (ie, BMI percentile <85th percentile) versus nonhealthy weight (ie, BMI percentile ≥85th percentile), and middle/low SES versus high SES. SES will be estimated using a composite score using the family income-to-needs ratio and parent education level [41] (described in detail in the "Demographics" section).

Blinding

The principal investigator (PI; JPM) and statistician will be blinded to the treatment condition. The outcome assessors will not be blinded to the condition. Selection bias in the unblinded study personnel will be minimized through the randomization procedure.

Conditions

Experimental Condition

The i♥rhythm project comprises five 15-minute sessions focused on (1) having consistent daily bedtimes; (2) providing opportunities for sunlight exposure during the day and minimizing exposure to artificial light at night; (3) providing opportunities for activity during the day so that the child is ready to fall asleep at night; (4) ensuring the last bite of food is 1-2 hours before bed; and (5) reviewing and developing of a maintenance plan.

Self-determination theory was used to guide adaptation of the behavior change components of the intervention [42]. Self-determination theory aims to promote sustained behavior change by emphasizing intrinsic motivation, in this case promoting the satisfaction of 3 basic psychological needs: autonomy (independence to choose to change behavior), competence (belief in one's ability to perform a behavior), and relatedness (alignment with one's core beliefs and values) [42].

The 5-week session intervention framework and flow are presented in Figure 2. The first 4 sessions will each involve a series of videos and multiple-choice questions that guide parents through the following: (1) identification of a value that is important to them as a parent, such as having a healthy child, being spiritual, being a role model, being responsible; (2) identification of a reason why they might want to encourage their child to have a regular bedtime that is consistent with the value they selected; (3) education regarding the topic of the week and relevance to promoting a consistent bedtime; (4) implementation intention in which parents set their intention for their child's bedtime that week and make an action plan for how they would achieve that bedtime goal utilizing skills that were introduced in the educational video; (5) identification of

potential barriers to achieving their action plan; and (6) development of a coping plan in the event they encounter the identified barriers. The final screen will contain a summary of their responses, links to additional resources, and an option to print the plan (Multimedia Appendix 1). In between sessions parents will monitor and record their child's bedtime. Daily light exposure, physical activity, and whether the child's last bite of food was 1-2 hours before bedtime will be monitored on an intermittent basis beginning the week the topic is introduced. The fifth session will review the 4 topics and guide families through the development of a maintenance plan using open-ended questions. A summary of the developed maintenance plan is provided to participants at the end of the session. The sessions have been developed and programmed on an online survey platform called Alchemer [43].

Considering the developmental abilities of children aged 5-8, parents are considered the primary agent of change, though child viewing of the videos is encouraged. Session links will be emailed to participants and posted to a private Facebook group on Sunday mornings beginning the first week of summer break. The private Facebook group serves to promote social support for parents and to provide parents access to additional resources through daily (Monday-Friday) posts (Table 2 contains an example week). The Facebook group will be administered and monitored daily by research staff who assisted in the development of the intervention. The PI (JPM) will meet weekly with the intervention delivery team to ensure the intervention is delivered according to protocol. To ensure the PI remains blinded, no participant identifying information will be used in these meetings.

Figure 2. Intervention framework.

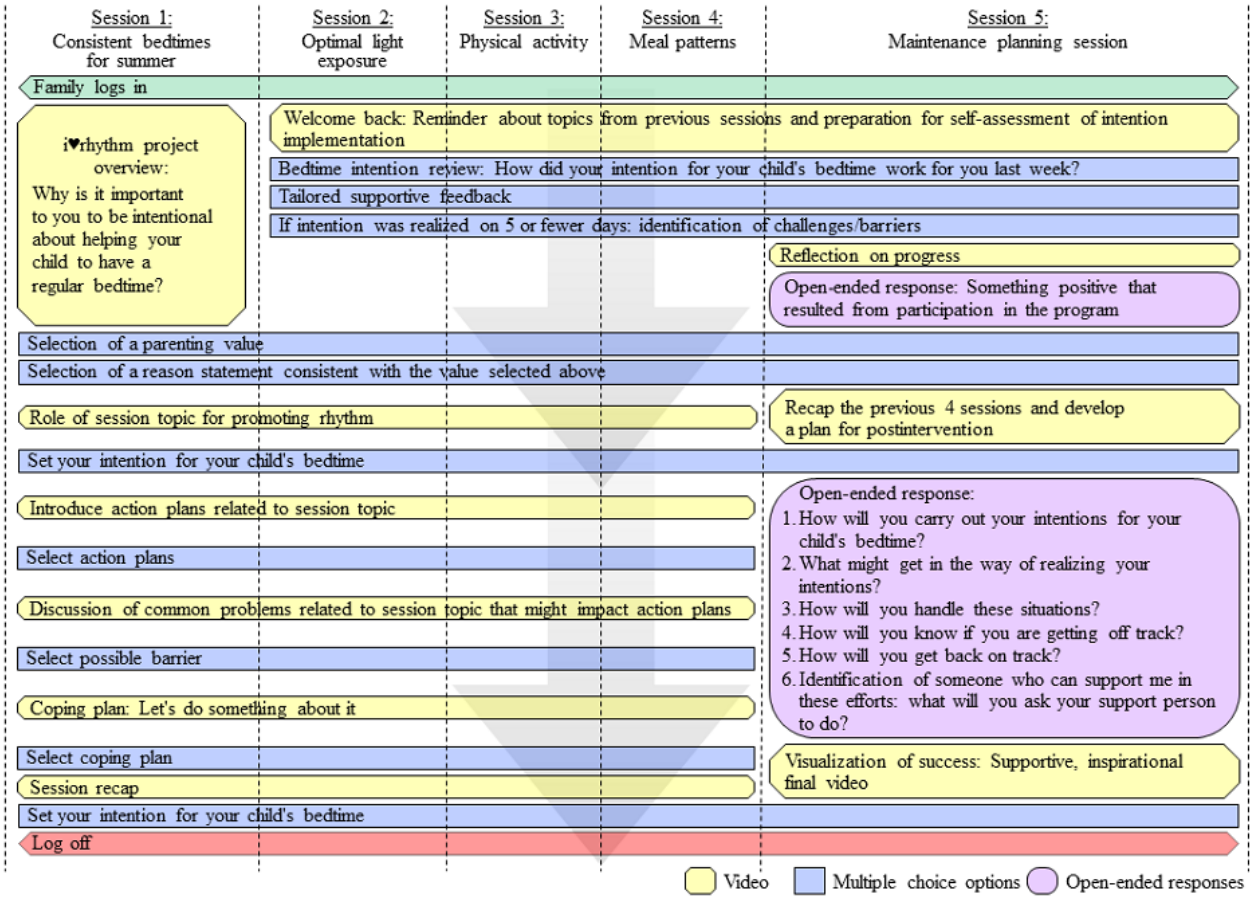


Table 2. Example week of Facebook posts.

Day	Themes	Topic	Text of the post
Sunday	Intervention Session	Session 1—Consistent Bedtimes	*Today's the day! Click on the link below to begin Session 1 of the i♥rhythm project. #sleep #consistencyiskey #bedtimeroutine*
Monday	Topic Introduction	Setting Up a Calming Bedtime Routine	*With long days and busy family schedules, how do you set up a calming bedtime routine for your child? Read this resource to learn more (link). If you have any issues accessing the Dropbox folder, please let us know. #sleep #bedtime routine*
Tuesday	General	Reminder About Resources	*Just a quick note that additional resources can be found in our Box folder (link). Over the next few weeks, we will be covering the following topics: Consistent Bedtimes, Light Exposure, Physical Activity, Meal Timing, and Maintenance. Remember to reach out if you have any questions! #resources*
Wednesday	Barriers and Solutions	Helping Your Child Fall Asleep Independently	*Is your child having trouble falling asleep independently? Click on the link to read about strategies to get your child's sleeping schedule back on track. If you have additional strategies to share, feel free to comment with them below!*
Thursday	Status Update	Check-in poll about progress	*What are some strategies that helped your child keep a consistent bedtime this week? For the poll, you can choose multiple options, add your own, or type it in the comments. Note: the results of the poll are not anonymous.*

Control

Control participants will not receive an intervention and will only participate in Time 0, 1, 3, and 4 assessments as outlined in Table 1.

Process Evaluation

Process evaluation documents intervention delivery and provides insight into the mechanisms by which programs work [44]. Following the framework of Baranowski and Jago [45], we will assess recruitment of participants, maintenance of participation, the context of implementation, resources necessary for implementation, implementation (completion of sessions, daily diaries, and engagement in social media), reach, barriers to implementation, and exposure to the program. Participant completion of sessions will be monitored via logins, video views, and completion of interactive content and diary data. Engagement in social media will be collected via manual abstraction from the newsfeed of the private group [46]. Other issues such as acceptability will be assessed by questionnaires after intervention. Postassessment interviews will examine (1) acceptability of the interventions, (2) perceived benefits of participation, (3) barriers to participation, (4) reasons for drop out. Following the intervention (Time 1) and final data assessment (Time 3), qualitative interviews will be conducted. Interviews will use a standardized script, open-ended questions, follow-up questions, prompts, and areas to probe. Interviews will be conducted until theoretical saturation is achieved [47,48]. Thematic data analysis will identify common themes and patterns [49]. Each statement will be assigned a broad category and assessed for meaning units, specific categories, and subcategories. These will be compared and contrasted by gender, overweight status, and SES level.

Adherence

Participant completion of sessions will be monitored by an outcome assessor (HD) who will send SMS text message reminders to the family if they did not complete a session within 2 days after the release of data. Families who miss a session will be sent the next session the following week. Facebook post views and engagement will also be monitored using metrics provided by Facebook.

Data Collection

Two weeks before the scheduled assessments, actigraphs will be mailed to the child's home. A link to an online instructional video will demonstrate proper wear and how to avoid covering the accelerometer with clothing [50]. Children will wear actigraphs (GT3X-BT; ActiGraph, LLC) on the wrist of their nondominant hand to assess their sleep and activity for 7 days and 8 nights during the school year. Parents will complete a daily sleep diary and monitor-wear logs to record the times the accelerometer is removed and the reason for removal [51-53]. A paper copy of these forms will also be provided for note-taking purposes. Parents will download an app called Centrepoint (ActiGraph, LLC) to their phone and will be asked to use this app to upload their child's actigraph data to the cloud via a Bluetooth connection. Download instructions will be emailed to participants and research staff will follow-up to provide a PIN. During this follow-up, the parent will perform a preliminary upload to verify data are transferring. The Centrepoint app will allow research staff to monitor participants' compliance with accelerometer wear and ensure sufficient wear time is achieved before coming into the sessions. Sufficient wear time will be defined as having at least five nights [51] and days of activity data. Valid days will be defined as at least ten hours of wear time in 24 hours [54]. As sleep will not be scored until after the actigraphs are returned, this determination will be made by research staff using visual inspection of the Centrepoint data. During the 8 days when the monitor is worn, parents will be asked to complete a web-based dietary food recall using the Automated Self-Administered 24-Hour Dietary Assessment Tool (ASA24) 3 times and complete a series of questionnaires (described below). Completion of the ASA24 will be monitored by the research staff. If the online diary status shows as incomplete, the parent is emailed the next day to complete another day of intake until 3 full days are complete.

The aim is to obtain dairy intake data for 2 weekdays and 1 weekend day.

Approximately 1-2 days following the eighth day of accelerometer wear, assessment visits will be scheduled. Participants will be scheduled to arrive at the laboratory at least six hours before their typical bedtime. Typical bedtime will be estimated using visual inspection of the actigraphy data in Centrepoint along with parent sleep diaries. On the day of the laboratory visit, participants will be asked to avoid intake of caffeine, chocolate, nonsteroidal anti-inflammatory drugs, and cannabidiol products. Upon arrival at the laboratory, anthropometric assessments will be conducted and actigraph data will be downloaded. Children and their parents will be taken to a dimly lit (<5 lux) circadian phase assessment suite (a private room with a table and chairs and a futon chair with an adjoining bathroom). Following established procedures with children, saliva (~1 mL) samples will be collected using untreated Salivettes (Starstedt, Inc.) every hour beginning 5 hours before and ending 1 hour following typical bedtime. Before the collection of samples, children will be seated for 10 minutes to minimize postural effects on melatonin concentration. If participants eat or drink before the sample collection, they will gently brush their teeth with a soft-bristled toothbrush and water. Saliva samples will be centrifuged and frozen for later analysis of melatonin. Assessment visits will end after the final saliva sample collection.

To compensate participants for travel and the inconveniences associated with assessments requiring a minimum stay of 7 hours in the laboratory and keeping children awake past their bedtime at each assessment, participants will be offered US $100 at Times 0 and 1 and US $150 at Times 2 and 3 to encourage participation in assessments.

Primary Outcomes

Feasibility Criteria

The feasibility of the study will be established by our ability to recruit the needed sample size and retain at least 80% of participants at Time 1 and 60% at Time 3. The feasibility of the intervention will be determined based on delivery of all components of the intervention as designed, favorable acceptability ratings by 80% of parents randomized to the experimental condition, completion of greater than 60% of daily self-monitoring, and views of 80% of intervention sessions by the experimental sample.

Treatment Acceptability

Participants assigned to the experimental condition will complete the Treatment Acceptability Report Form-Revised (TARF-R) at Time 1. The TARF-R is a 20-item global measure of treatment acceptability for behavioral interventions. Examples of items include (1) “How clear is your understanding of this intervention?”; (2) “How acceptable do you find the intervention to be for you and your child?”; (3) “How reasonable do you find the intervention to be?”; (4) “How likely is the intervention to make improvements in your child’s health habits?”. The TARF-R has demonstrated good internal consistency (αs>.69) and evidence of construct validity (reference). A favorable rating is considered 4 or greater.

Anthropometrics

While feasibility criteria will serve as a primary outcome for this study, change in BMI will serve as the primary outcome for the fully powered randomized controlled trial. BMI is the most common indicator of body size and has been consistently correlated with metabolic problems in children. Participants’ height and weight will be measured. Weights will be assessed in light clothing without footwear using a Healthometer digital scale. BMI (kg/m^2) will be computed and BMI percentile and standardized BMI will be calculated from age and gender normative data. BMI percentile will determine the weight status group. Based on baseline BMI percentiles, children will be classified into 3 weight categories: healthy weight (5th percentile to <85th percentile for BMI), overweight (≥85th to <95th percentile for BMI), and obese (≥95th percentile for BMI). Change in BMI and standardized BMI are the best proxy measures for change in fat mass and standardized fat mass, respectively, and will assess exploratory hypotheses.

Circadian Phase

While feasibility criteria will serve as the primary outcome for this study, circadian phase will serve as a primary outcome for the fully powered randomized controlled trial. Circadian phase can be examined by measuring the timing of melatonin onset under dim light conditions (DLMO). Compared with markers of endogenous circadian rhythms, melatonin is relatively robust [55,56]. Salivary DLMO measures have demonstrated high intraclass correlations (0.93) with plasma and sensitivity and specificity comparable to plasma assays [57]. Saliva samples will be analyzed using radioimmunoassay test kits (NovoLytiX GmbH) at SolidPhase, Inc. The DLMO phase will be determined using linear interpolation across the melatonin concentration values detected in the saliva samples before and after concentration levels increase to and remain above 4 pg/mL [58,59]. The DLMO phase or the time at which melatonin levels rise and remain above 4 pg/mL will be used to compare differences in the circadian phase across conditions.

Secondary Outcomes

Body Composition

Total body fat and percent body fat will be assessed using air-displacement plethysmography (BOD POD; COSMED USA, Inc.). Participants will enter the chamber wearing a 1-piece swimsuit and swimming cap. The procedure will be conducted twice for 45 seconds. If a difference greater than 150 mL between body volumes is detected, then a third measurement will be collected. The thoracic gas volume will be estimated using the BOD POD software (BOD POD GS-X) [60]. Body density will be calculated by dividing the raw body mass (kilogram) by the corrected body volume (liter). Fat-free mass, fat mass, and percent body fat will be derived from body density using the Siri equation [61].

Actigraphy

Actigraphs (GT3X-BT) worn on the wrist of the dominant hand 24 hours a day for 7 days will measure sleep duration, the timing of sleep onset, and waking as well as physical activity and light exposure. Using the Sadeh algorithm [62] epochs will be scored

as sleep or wake. According to established protocols [17,63], each sleep episode reported in the parent diary will be inspected in the activity data. Nights will be considered valid if the participant provided 20 minutes of wear time before sleep onset. Nonwear time in the hour before bedtime must be less than 60 minutes unless confirmed by the wear log, or unless ambient light data are available to confirm bedtime. Sleep onset will be defined as the beginning of the first 3 consecutive epochs scored as sleep. Sleep offset will be defined as the last 5 consecutive minutes of sleep occurring before 15 minutes after the reported wake-up. Sleep midpoint will be defined as the midpoint between sleep onset and offset. Children's physical activity will be measured using vector magnitude activity counts captured in 60-second epochs and categorized into sedentary, light, moderate, and vigorous physical activity using established cut points [64].

Dietary Assessment

The ASA24 [65] will be used to assess children's dietary intake, including total daily caloric intake, the timing of intake, timing of the last eating episode of the day, and caloric intake of the last eating episode. As recommended, parents will complete the ASA24, providing a proxy report of their child's dietary intake [66]. Investigators will use 3 days of diet assessment as this optimizes the prediction of doubly labeled water-estimated energy expenditure [67]. The ASA24 will be used to assess average daily caloric intake. Average caloric intake in the morning (6:00 AM to <10:00 AM) and nighttime (7:00 PM to <6:00 AM) will be calculated using defined criteria [68] along with the timing of the first and last eating episode of the day.

Covariates

Demographic Information

Parents will report on their own and child's date of birth, sex, ethnicity, and race. The SES will be assessed using the family income-to-needs ratio [69]. This metric considers the family income level in relation to the number of individuals supported by the income level [41]. Parents will report annual familial income according to the following categories: US $10,000 to US $20,000; US $20,000 to US $35,000; US $35,000 to US $50,000; US $50,000 to US $75,000; or more than US $75,000. The mean of the reported income level will be divided by the federal poverty threshold for a household of that size [69]. Ratios with a value less than 1 will be assigned a value of 1=1 (poverty), 1-2=2 (living near the poverty line), 2-3=3 (lower middle class), 4=4 (middle class or higher) [41]. Parent education will be reported according to the following categories: seventh grade or less, completion of eighth grade, ninth to eleventh grade, high-school graduate, partial college or specialized training, bachelor's degree, or graduate degree. These education categories will be assigned scores on a scale of 1-7, respectively. A composite score will be created by adding together the income-to-needs ratio level with the parent education level to create a composite score [41]. Values of 8 or lower will be considered middle/low SES and values of 9 and 10 will be considered higher SES.

Parenting Structure

The Comprehensive General Parenting Questionnaire (CGPQ) is a parent report of parenting practices among parents of 5-13-year olds [70]. Investigators will assess subscales related to parenting structure (Inconsistent Discipline, Consistency, Organization, and Scaffolding). There is support for the construct validity of the CGPQ [70]. Parenting structure subscales have demonstrated acceptable internal reliability (ranging from 0.67 to 0.74) [70]. Subscale scores range from 5 to 25. Higher scores indicate higher levels of structure.

Bedtime Routines

The Bedtimes Routines Questionnaire (BRQ) is a 31-item parent report measure of children's bedtime routines comprising 3 scales measuring the consistency of bedtime routines (weekday and weekend), reactivity to changes in bedtime routines, and frequency of adaptive and maladaptive activities [71]. The BRQ scales have acceptable internal consistency (α) ranging from .69 to .90. Scores on the Consistency and Adaptive Behavior subscales range from 10 to 50, with higher scores reflecting more consistent bedtime routines and higher. The Reactivity scale scores range from 5 to 25, with higher scores reflecting greater reactivity. The Maladaptive Behavior scale has possible scores ranging from 6 to 30 with higher scores reflecting more maladaptive behaviors [71].

Summer Care Arrangements

Children's involvement in summer school, childcare, entertainment programs, as well as day or overnight camps will be assessed by a parent report survey based on a modified version of the Early Childhood Longitudinal Program Kindergarten Class's parent interview on summer activities [72].

Stress (Parent)

The 10-item Perceived Stress Scale (PSS-10) is a self-report measure of the parent's perceived stress with established acceptable psychometric properties (αs >.70, test-retest criterion coefficient >0.7, validated factor structure, and evidence of convergent validity) [73]. Scores range from 0 to 40, with higher scores reflecting higher levels of perceived stress.

Social Support (Parent)

Interpersonal Support Evaluation List (ISEL) is a 12-item self-report measure of the parent's perceived availability of social support [74]. The "Tangible" subscale assesses perceived availability of resources and material aid; the "Appraisal" subscale assesses the perceived availability of another individual(s) to discuss one's problems; the "Self-esteem" subscale assesses the perceived availability of someone to compare one's self to in a positive manner; and the "Belonging" subscale assesses the perceived availability of having others to socialize and do things with. Scores range from 0 to 30 on each scale, with greater scores indicating higher levels of social support [74].

Treatment Motivation

Participants assigned to the experimental condition will complete13 items regarding their motivation to follow the

procedures of the program and to remain in the program. Items were adapted from [75,76].

Data Management

A manual of procedures, including protocols related to the collection of each measure and storage, was developed at the beginning of the study. In 2021, before the beginning of data collection, an in vivo training session was scheduled and all data collectors took turns practicing all assessment protocols, and feedback was provided by the PI (JPM) and senior coordinator (HD). The manual of procedures will be maintained and continually updated with input from all related study coordinators. Weekly meetings will be held with the PI and study coordinators to review recruitment, study progress, and data storage and management.

Data Analysis Plan

A statistical analysis plan will be written before the database is locked and breaking the blind. The feasibility of the intervention will be assessed from staff-collected and parent-reported variables according to the previously stated criteria. We will examine the internal consistency of all questionnaires using Cronbach alpha. Decisions regarding the need for changes before further testing of the intervention will be made based on the attainment of feasibility criteria and postassessment interviews. This pilot study is not powered to detect differences in outcome variables and therefore drawing conclusions about the efficacy of the intervention based on statistically insignificant differences in change in BMI, standardized BMI, or circadian phase is inappropriate [30,77-79]. Descriptive statistics and confidence intervals will be used to examine mean differences and the effect sizes of change in outcome variables between conditions. Exploratory analyses will be used to estimate intervention effect over time using a repeated-measures regression approach while controlling for sex and SES, and accounting for the within-subject correlation and the nesting of children within families. The model will include a fixed effect for the repeated measurements (Times 0, 1, 2, and 3), a random subject effect, and treatment group as a between-subjects factor (i♥rhythm and control). Children's differences across the groups in change in BMI, standardized BMI, and circadian phase will be tested using a group × time interaction. Change in BMI was included as an outcome because it is considered the preferred measure of change in adiposity among children over periods of less than 1 year [80-82]. Separate models will examine other dependent variables of interest including sleep duration, the timing of sleep onset, and interdaily similarity. Because the study is not powered to detect group differences in outcomes, effect sizes will be examined based on the standardized mean difference (Cohen *d*) criteria for small (0.20), medium (0.50), and large (0.80) [83,84].

Ethics Approval

This study was approved by the institutional review board at Baylor College of Medicine (approval number H-47369).

Results

This protocol was written following the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 statement for clinical trial protocols [85,86]. The trial was supposed to begin in the Spring of 2020; however, the trial onset was delayed 1 year as new human subjects research was halted by Baylor College of Medicine in the spring of 2020 due to the COVID-19 pandemic. As a result, recruitment began in March 2021. As of March 2022, data collection and recruitment are ongoing. Data collection is anticipated to end in September 2023. Amendments to the protocol will be made on ClinicalTrials.gov. Results will be communicated via publication and ClinicalTrials.gov.

Discussion

Overview

Summer is a time during which children's risk of obesity increases substantially [28,87]. Disrupted sleep patterns and behavioral rhythms, which may occur in the transition from the school year to summer vacation [6,15,16], have been implicated in the onset of obesity [7-9]. IPSRT is an evidence-based treatment for bipolar disorder that has demonstrated efficacy to prevent the reoccurrences of mood disturbances by preventing the misalignment of endogenous circadian rhythms through the promotion of stable behavioral rhythms (eg, sleep and meal patterns) [20]. The i♥rhythm project is an adaptation of IPSRT as an mHealth intervention to promote stable behavioral rhythms in children during summer vacation for the prevention of summer increases in BMI.

This study is a randomized controlled trial designed to evaluate the feasibility, acceptability, and preliminary efficacy of the i♥rhythm project to prevent accelerated summer weight gain. It is hypothesized that a priori feasibility criteria will be met and the intervention and assessment protocol will be found to be acceptable by participants. As this is a feasibility study, it is not powered to detect differences between groups; however, we anticipate that participants in the treatment condition will have circadian phases that trend toward being earlier and changes in BMI will tend to be smaller compared with participants in the control condition.

Strengths of this study include a rigorous design involving randomization, a comparator condition, and multiple follow-up assessments. Our hypotheses and outcomes have been stated a priori and criteria for evaluating the feasibility and acceptability of the study have been established. Additionally, procedures for process evaluation, intervention fidelity, and assessment of intervention adherence have been developed.

Limitations

This is a feasibility study and is not powered to detect differences in circadian phase, sleep, or BMI outcomes. If deemed feasible in this study, a fully powered randomized controlled trial will be needed to determine the efficacy of this approach. The current research is being conducted during the COVID-19 pandemic. Due to the halting of new human subjects research in the spring of 2020, the trial onset was delayed by 1 year. The initial phase of recruitment (March-May 2021) began at the end of the second COVID-19 wave (2021) and Time 1 (postintervention assessments) ended just as the Delta wave was beginning in August 2021. For many children, the

2020-2021 school year may not have been typical. Many children may not have attended school in person, potentially weakening the effect of school-summer differences. The 2021-2022 school year has been more typical in the sense that most children returned to school in person. While there is evidence that the pandemic has exacerbated the obesity epidemic in children [88,89], the extent to which patterns of improvement in school-year weight outcomes and accelerated summer weight gain have persisted during the pandemic is unclear. Vaccines became available to 5-8-year olds in November of 2021. The next phase of recruitment will begin as the Omicron-fueled wave appears to be declining (February 2022). It is unclear the extent to which the pandemic has affected our ability to recruit and retain families in the study.

Conclusions

This study seeks to prevent child obesity by combining 2 distinct intervention concepts (enhanced sleep and stable behavioral rhythms) that have previously not been combined for the prevention of childhood obesity. This represents a departure from traditional obesity prevention approaches that have focused on the simple energy balance of diet and physical activity [5]. The proposed research aims to expand our understanding of the role of sleep and behavioral rhythms in the prevention of childhood obesity and adapting IPSRT for children should result in an innovative evidence-based approach to promoting stable behavioral rhythms for obesity prevention. In addition, this study focuses on summer, a time when young children experience significant increases in BMI [90,91]. To our knowledge, the proposed research is the first to (1) provide preliminary evidence regarding the impact of an intervention for the prevention of increases in BMI during summer and the longer-term impact on weight status, (2) combine 2 distinct theories regarding the obesogenic role of sleep and behavioral rhythms among children, and (3) examine a novel adaptation of an evidence-based treatment of bipolar disorder for the prevention of childhood obesity.

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Authors' Contributions

JPM conceived of the intervention concept and study design. HD assisted with the drafting of the manuscript. SM advised the randomization procedures and data analysis plan. TB, DT, CAA, and SJC provided critical input on the development of the intervention concept and study design. All authors reviewed and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Intervention screenshots.
[PPTX File , 192 KB - resprot_v11i5e37002_app1.pptx]

Multimedia Appendix 2
Peer-reviewer report from the Pediatrics Subcommittee - Eunice Kennedy Shriver National Institute of Child Health and Human Development (CHHD-A) Initial Review Group (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 168 KB - resprot_v11i5e37002_app2.pdf]

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Abbreviations

ASA24: The Automated Self-Administered 24-Hour Dietary Assessment Tool
BRQ: Bedtimes Routines Questionnaire
CGPQ: Comprehensive General Parenting Questionnaire
CNRC: Children’s Nutrition Research Center
DLMO: dim light melatonin onset
IPSRT: interpersonal and social rhythm therapy
ISEL: Interpersonal Support Evaluation List
mHealth: mobile health
PI: principal investigator
PSS-10: 10-item Perceived Stress Scale
SES: socioeconomic status
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TARF-R: Treatment Acceptability Report Form-Revised

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Protocol

Cardiovascular Disease Prevention Education Using a Virtual Environment in Sexual-Minority Men of Color With HIV: Protocol for a Sequential, Mixed Method, Waitlist Randomized Controlled Trial

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Abstract

Background: It is estimated that 70% of all deaths each year in the United States are due to chronic conditions. Cardiovascular disease (CVD), a chronic condition, is the leading cause of death in ethnic and racial minority males. It has been identified as the second most common cause of death in persons with HIV. By the year 2030, it is estimated that 78% of persons with HIV will be diagnosed with CVD.

Objective: We propose the first technology-based virtual environment intervention to address behavioral, modifiable risk factors associated with cardiovascular and metabolic comorbidities in sexual-minority men of color with HIV.

Methods: This study will be guided using social cognitive theory and the Technology Acceptance Model. A sequential, mixed method, waitlist controlled randomized control feasibility trial will be conducted. Aim 1 is to qualitatively explore perceptions of cardiovascular risk in 15 participants. Aim 2 is to conduct a waitlist controlled comparison to test if a virtual environment is feasible and acceptable for CVD prevention, based on web-based, self-assessed, behavioral, and psychosocial outcomes in 80 sexual-minority men of color with HIV.

Results: The study was approved by the New York University Institutional Review Board in 2019, University of Texas Health Science Center at Houston in 2020, and by the Yale University Institutional Review Board in February 2022. As of April 2022, aim 1 data collection is 87% completed. We expect to complete data collection for aim 1 by April 30, 2022. Recruitment for aim 2 will begin mid-May 2022.

Conclusions: This study will be the first online virtual environment intervention for CVD prevention in sexual-minority men of color with HIV. We anticipate that the intervention will be beneficial for CVD prevention education and building peer social supports, resulting in change or modification over time in risk behaviors for CVD.

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KEYWORDS

virtual environment; behavioral intervention; consumer health informatics; HIV; cardiovascular disease; sexual minority men; prevention education; gamification; health communication

Introduction

Background

In the United States, it is estimated that more than 70% of all deaths each year are due to chronic illness. [1,2] HIV, a blood-related chronic illness, disproportionately affects racial and ethnic minority groups, specifically African American and Latino sexual-minority men [3,4]. In alignment with the National Institutes of Health Sexual and Gender Minority Research Office, we use the words "sexual-minority men" to refer to nonheterosexual persons who identify as gay, bisexual, or queer, or persons having same-gender or same-sex attractions or behaviors.

Approximately 150 million persons are living with at least one chronic illness, and close to 30 million persons are living with 5 or more chronic conditions [5]. The chronic illness with the highest prevalence in ethnic and racial minority populations is cardiovascular disease (CVD). Cardiovascular disease is the leading cause of death in ethnic and racial minority males [6]. In 2016, it was estimated that CVD mortality among ethnic and racial minority groups was highest in African American adults. Moreover, more than 50% of Latino males aged 20 years and older had CVD. CVD risk may be lowered by following modifiable lifestyle strategies. However, HIV is an additional risk factor that increases CVD risk in African American and Latino men. Epidemiologic reports have suggested that half of African American sexual-minority men and a quarter of Latino sexual-minority men in the US will be diagnosed with HIV in their lifetime [7], demonstrating the urgency of prevention efforts in this population.

CVD has been identified as the second most common cause of death in persons with HIV, and research suggests that overall CVD awareness in the general public is inadequate [8]. By 2030, (8 years after this protocol's publication year of 2022), it is estimated that 78% of persons with HIV will be diagnosed with CVD [9].

Cardiovascular and metabolic health disparities add to an already disproportionate HIV burden [10-13]. Persons with HIV are at higher risk of CVD than HIV-negative persons [14] as a result of chronic inflammation, certain antiretroviral therapies, and other risks, such as tobacco use [12,15-17]. Persons with HIV often lack social supports, live in low-resource communities, and have limited financial resources, exaggerating cardiovascular health disparities [18-20].

Disparities in Accessing Health Care

Stigma, fear, and discrimination have led to underutilized health care. Previous work has substantiated some root causes of HIV health disparities as being individual- and structural-level factors [21-24]. These factors include perceived racism, sexual identity discrimination [25], and health care provider discrimination, which combine to impact treatment access and usage [21-23]. These barriers work to perpetuate silos in which sexual-minority men utilize their social networks for support and information on how to best care for their illnesses. As a result, the cumulative effects of living with HIV and not having access to equitable health care and prevention information, compounded by the increased risk of CVD, can be profoundly life threatening. If strategies and interventions to increase cardiovascular health equity in persons with HIV are not prioritized, persons with HIV will continue to experience increased morbidity, mortality, and a substantially decreased quality of life [26].

The Promise of Prevention Education Using a Virtual Environment

Ubiquitous computing, the availability and usage of technology everywhere, has changed the paradigm of traditional in-person, face-to-face clinical interactions. Accordingly, research has shifted toward utilizing health technology as a means to promote healthy behaviors and lifestyle changes [27] via tablets, smartphones, portable trackers, and web-based interventions that use gamification [28]. Gamification using a virtual platform can increase motivation and improve user engagement, fostering health-enhancing behaviors [28,29]. Virtual environments hold much promise given their broad appeal to people of different ages, backgrounds, and levels of technological experience [30]. Research has documented the benefits and positive outcomes of using virtual environments for interventions focused on diabetes self-management [30-32], smoking cessation [33,34], HIV medication adherence [35], and prevention of risk behaviors for HIV in sexual-minority men [36,37]. They can be customized to focus on specific diseases, and content can be developed that is tailored for persons with HIV by including information on cardiovascular and metabolic disease prevention [38]. An additional benefit of using a virtual environment is anonymity. Anonymity can decrease barriers to engagement with virtual environment content and also allows individuals to speak more freely, without having to worry about someone identifying who they are [30,39]. Using an anonymous virtual environment also facilitates access to reliable prevention education and can support health-enhancing behaviors that can be transferred to

real-world encounters [30]. The virtual environment can also facilitate social networking with other participants [40,41] and with health educators [37], which can build up a social support structure. This approach may prove more engaging for sexual-minority men of color, without the stigma that can be associated with face-to-face encounters [42].

Study Objectives

Building on the Learning in a Virtual Environment (LIVE) intervention [30-32,38], we propose the first technology-based virtual intervention to address behavioral, modifiable risk factors associated with cardiovascular and metabolic comorbidities in African American and Latino sexual-minority men. Our study aims to (1) explore concerns, management, perceptions of risk, and prioritization of HIV-related comorbidities among sexual-minority men with HIV; (2) test the feasibility, acceptability, and preliminary effects of a virtual environment to address prevention of HIV-related CVD based on behavioral and psychosocial outcomes; and (2a) characterize the social network structure and usage behaviors of the participants using process data from the virtual environment. We anticipate that using a virtual environment for CVD prevention education will be advantageous to sexual-minority men of color, as it may facilitate health-promoting behaviors through education and peer social support.

Methods

Conceptual Framework

This study will be guided by social cognitive theory and the Technology Acceptance Model. Both models have wide usage in health communication interventions. Social cognitive theory posits that bidirectional relationships exist between person, environment, and behavior. Behaviors are learned by modeling or by observation of others [43]. We will implement modeling and observation through participant interaction with a live health educator and other peer players in the virtual environment. We anticipate the virtual environment will be used to empower participants with prevention education, skills, and increased access to social supports to facilitate health-promoting behaviors that can be translated back to activities in their daily lives for prevention of CVD. The Technology Acceptance Model is a consumer health informatics model used for determining an end user's acceptance of technology and their intent to use a specific technology [44]. We will measure "perceived usefulness" and "perceived ease of use," as both constructs are influential to attitudes and acceptance [45] of the virtual environment for CVD prevention education. We anticipate that if the virtual environment is useful and easy to use, this may be an antecedent to facilitating behavior change and health-promoting behaviors.

Design

We will conduct a 2-phase, exploratory, sequential mixed methods study with a waitlist controlled clinical feasibility trial. The protocol is registered on ClinicalTrials.gov (NCT05242952) and was approved by the institutional review boards at New York University, Yale University, and the University of Texas Health Science Center at Houston.

Eligibility

In order to meet enrollment criteria, participants must (1) be a cisgender male between ages 30 and 65; (2) identify as an ethnic or racial minority; (3) have HIV; (4) identify as gay, bisexual, or queer; (5) read and understand English; (6) have access to a computer capable of downloading and running the virtual environment software; and (7) have no cognitive impairment and no medical history of serious complications, such as myocardial infarction, congestive heart failure, coronary artery bypass graft, or cerebral vascular accident. It is documented that the highest incidence of HIV is among emerging adults (ie, up to 34 years old) [46], as chronic illness is becoming diagnosed at earlier stages of life (eg, 18 to 30 years old) with the highest prevalence at age 50 years and older [47]. Our sample age range is appropriate given the changing age demographic of chronic illness and will provide a thorough overview spanning 3 generations.

Ethics Approval

All procedures performed in studies involving human participants are in accordance with the ethical standards of the institutional and national research committee, the 1964 Helsinki Declaration and its later amendments, or comparable ethical standards. The study was funded by the National Heart, Lung, and Blood Institute (K01HL145580) and approved by the New York University Institutional Review Board in 2019 (IRB-FY2018-2284), the University of Texas Health Science Center at Houston in 2020 (HSC-SN-20-1143), and by the Yale University Institutional Review Board in February 2022 (2000031403). Informed consent has been obtained from all individual participants who have participated thus far. We will obtain informed consent from all individuals who meet the eligibility criteria and want to participate.

Recruitment

To increase the feasibility of participant enrollment and data collection and to use existing resources more efficiently, we will utilize a preexisting HIV registry and employ respondent-driven sampling for aims 1 and 2. Respondent-driven sampling is an ideal approach to purposively draw participants that are similar because of their connections (eg, having HIV, identifying as a sexual-minority male, and having ethnic or racial minoritized heritage), known as homophily [48-50]. This approach is fitting as a potential preemptive when recruiting historically under-sampled communities [51,52]. To prevent enrollment shortfalls, we will also partner with community-based organizations who serve LGBTQ+ populations in the New York City area. Zoom (Zoom Video Communications, Inc) will be used as the primary method of communication for enrollment, orientation to the study, and data collection in aim 1.

Procedures

The overall purpose of this study is to prevent CVD health disparities in sexual-minority men of color with HIV using a virtual environment, which to our knowledge has not been done before. We will use the LIVE platform, a preexisting, disease-agnostic (ie, it can be modified and reused for any chronic illness) [38] virtual environment to conduct the study.

To address aim 1, qualitative interviews will explore participant perceptions of health concerns. Participants will be compensated with a $30 gift card for completion of the interview. Aim 2 will be addressed in an iterative multiphase approach. In phase 1 of aim 2, beta testing will be conducted with a subset of 10 intended users to assess if the platform is embedded with relevant information and to ensure there are no technical issues. Our beta testing approach and sample size follow published recommendations [53,54]. Beta testers will receive $30 for their time. In phase 2, the LIVE platform will be used to conduct a waitlist controlled feasibility clinical trial with 80 sexual-minority men with HIV. Participants will be compensated with a $30 gift card at 3 timepoints (baseline, 3 months, and 6 months) for a total of $90 for completion of aim 2, phase 2. Subaim 2a includes collection of process data from participants. We will analyze this data to determine feasibility, usage, and acceptability. Using the LIVE platform will be advantageous to extend the utility of virtual technology to populations that are underrepresented, stigmatized by chronic illness, and at high risk for CVD. The virtual environment waitlist control clinical feasibility trial will run over a 12-month period (6 months for each group), which is an acceptable amount of time to collect preliminary data.

Intervention Fidelity

The study staff will include the principal investigator, a research assistant, a health educator, and student volunteers. All study personnel will have completed ethical research training using the Collaborative Institutional Training Initiative online courses. We will address five components of intervention fidelity in this trial: (1) intervention design; (2) study staff training; (3) intervention delivery; (4) participant receipt of intervention; and (5) assessment of intervention outcomes. To address intervention fidelity of the study design, we have included alternative strategies for potential setbacks, such as collaborating with community-based organizations in New York City. To ensure that all study staff administer messaging and the intervention in the same manner, the principal investigator will hold training prior to the start of the intervention and periodically throughout the intervention to mitigate potential deviations from the protocol. For example, study personnel will engage in participant recruitment and enrollment roleplaying. They will practice describing the study and answering questions related to the study, and they will also be trained in how to obtain informed consent for study participation. In order to ensure standardization and replication of the intervention, we will be using standardized measures to examine outcomes. We have also developed a scope of work document that describes the processes and flow of the research-related tasks and responsibilities. It includes a script for recruiting participants. We also developed a table of contents for the live health educator sessions. This is to ensure that structured prevention education on cardiovascular health–related topics is included. Participant receipt of the intervention will be measured in aim 2 using process data, such as logins, objects clicked, time spent, areas visited, and engagement with other participants online. We will also conduct a brief postintervention assessment with a subset of participants to qualitatively assess knowledge and skills gained and applications of that knowledge and those skills to daily life.

Orientation to the Virtual Environment

All participants enrolled in the clinical trial will receive training from the principal investigator or study personnel on how to log in to the virtual environment, create a customized avatar, and use the Zoom platform. The virtual environment will be accessed by participants through their desktop or laptop computer using an online internet connection. Participants will be given a USB headset with a microphone to plug into their home computer to allow communication and listening while engaged in the virtual environment. We recommended usage of the virtual environment at least 3 to 4 times a week. Validated self-report measures will be collected using REDCap (Research Electronic Data Capture; a online software platform created by Vanderbilt University) at baseline, 3 months, and 6 months (Table 1).

Table 1. Measures and outcome assessments.

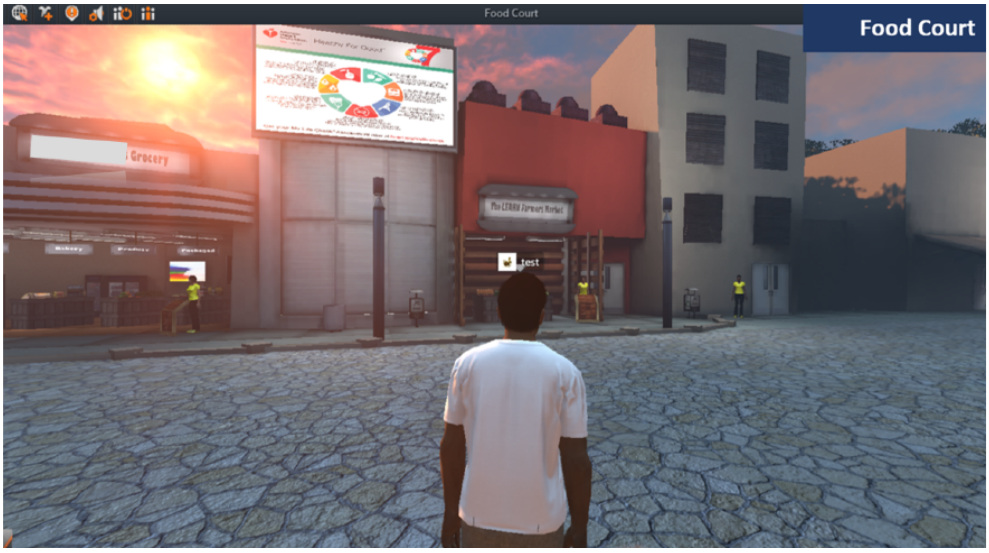
Measures	Outcome assessments	Baseline	Three months	Six months
Demographics	Demographic data (age, race, ethnicity, education, and income).	✓		
Life's Simple 7 [55]	Seven cardiovascular health metrics (blood pressure, total serum cholesterol, hemoglobin A_{1c}, smoking, BMI, physical activity, and The Healthy Eating Index, scored according to 3 levels of cardiovascular health.	✓	✓	✓
Perceived Usefulness and Perceived Ease of Use [44]	Based on the Technology Acceptance Model. Outcomes include perceived usefulness (Cronbach α of .98) and perceived ease of use (Cronbach α of .94) with an online 7-point Likert scale that is modified for the virtual environment.		✓	✓
Patient Health Questionnaire-9 [56]	Nine-item reliable and valid measure of depression severity (Cronbach α of .89).	✓	✓	✓
The Revised Illness Perception Questionnaire [57]	Illness perceptions about hypertension and type 2 diabetes on a 5-point Likert scale ("strongly disagree" to "strongly agree") (Cronbach α of 0.77 to 0.89).	✓	✓	✓
International Physical Activity Questionnaire Short Form [58-60]	Intensity of physical activity and sitting time using a 7-item, open-ended measure (Cronbach α of 0.80).	✓	✓	✓
Behavioral Risk Factors Surveillance System Questionnaire [61-63]	National behavioral risk data tool used by the Centers for Disease Control and Prevention, Health Resources and Services Administration, Veterans Administration, and the Substance Abuse and Mental Health Services Administration. Questions pertain to tobacco use and e-cigarette use (7 questions) (κ statistic of 0.81-0.92).	✓	✓	✓
Food Frequency Questionnaire [64,65]	Multifactor screener that assesses intake of fruits and vegetables, percentage of energy from fat, and intake of fiber. The screener asks respondents to report how frequently they consume foods in 16 categories. This screener has demonstrated correlations of 0.5 to 0.8 with estimated true intake.	✓	✓	✓

Intervention

The intervention, named Leveraging A Virtual Environment (LEARN) to Enhance Prevention of HIV-related Comorbidities in At-risk Minority Men Who Have Sex With Men, is adapted from a multisite, randomized controlled trial, Diabetes Learning in a Virtual Environment-LIVE [32,66], which was developed and is owned by authors CJ and AV. The LIVE study was a theoretically grounded platform created to support diabetes self-management and facilitate social support using a disease-agnostic environment [38]. In the current proposal, we focus on using a virtual environment for CVD prevention education in persons with HIV. The virtual environment infrastructure is composed of districts where participants can engage with content, such as a pharmacy (Figure 1) or grocery store (Figure 2). Gamification will be used to engage participants and provide motivation to utilize all embedded resources. Participants will interact with other players, complete quests to test their cardiovascular health knowledge, and obtain education on cardiovascular and metabolic comorbidity prevention. Additionally, participants will interact using synchronous voice and text. It is recommended that participants use the virtual environment at least 3 to 4 times a week. We anticipate this will facilitate the establishment of social support in a safe and anonymous online environment [39]. A health educator, trained in the study's procedures, will facilitate a 1-hour class that will provide cardiovascular health skill-building resources to participants. This will occur monthly over the course of data collection.

Figure 1. Pharmacy in the lobby.

Figure 2. Grocery store in the food court.



Aim 1

In aim 1, we will qualitatively explore concerns, perceptions about risks, and management and prioritization of HIV-related comorbidities in Zoom meetings with a sample of 15 sexual-minority men of color with HIV. The qualitative interviews are expected to contribute fundamental knowledge to the adaptation of the virtual environment. A qualitative interview guide with 5 open-ended questions will be used. The data obtained will be applied to the resources and to modification of the virtual environment. For example, if hypertension is a prominent concern, we will embed resources focused on reducing high blood pressure. We will also include these and other topics in a curriculum of presentations that the health educator will administer. After completion of aim 1, we anticipate that salient illnesses will be identified and subsequently embedded in the virtual environment. However, because of the diversity of participant ages, we expect to obtain heterogeneous descriptions of comorbidities that are of concern. In the unlikely event that a diverse list of concerns is not obtained, we will embed additional chronic conditions with the highest documented incidence and prevalence in persons of color into the virtual environment. This will help to address any under-identified chronic conditions that persons with HIV may be at risk for.

Aim 2

In aim 2**,** we will test the feasibility, acceptability, and preliminary effects of the virtual environment to address prevention of CVD comorbidities based on behavioral and psychosocial outcomes in 80 sexual-minority men of color. In order to test this, a waitlist controlled clinical feasibility trial will be conducted. The waitlist design is advantageous for three reasons: (1) recruitment, engagement, and retention will be enhanced by the ability to offer the intervention to all participants; (2) the waitlist control group can receive a version of the intervention improved by addressing any feasibility issues identified in the initial experimental group (ie, the design permits a second iteration of feasibility testing); and (3) the 2-group randomized design yields robust data for estimating group differences in change over time for study outcomes, [67] which will inform a subsequent large-scale grant. Permuted blocks

randomization with varying block sizes will be used to ensure allocation concealment and balanced allocation to the intervention and control groups over the study period [68]. Based on augmented reality research by Bailenson and colleagues [69], we anticipate that participants will be more prepared and equipped to apply what they have learned in the virtual environment to everyday life. Although using the virtual environment may seem intuitive, there is a remote possibility that participants may experience technological barriers. As part of the study, we will include a frequently asked questions brochure and contact numbers for technical support.

Subaim 2a

The purpose of subaim 2a is to characterize the social network structure and behaviors using process data obtained in the virtual environment. We will collect continuous process data from recording and tracking of all interactions within the virtual environment. We expect that the process data will reveal disarticulated patterns, behaviors, and utilization of networks, and show the structure of these networks as they are used by participants in obtaining information [50]. This is important, as the data will be used to identify how social processes affect behavior change [70] and leverage these networks to influence new social norms and behaviors [70]. In the unlikely event that there are technical issues during participant usage, information technology professionals who have designed and worked on LIVE for many years will be available to assist the study team.

Sample Size Calculation

The purpose of this study is to test the feasibility and acceptability of a virtual environment and obtain preliminary estimates of potential effects on behavioral and psychosocial outcomes in the prevention of cardiovascular comorbidities in persons with HIV. This is not a definitive test of intervention efficacy. Previous research has shown that feasibility studies with a sample size of at least 10 are sufficient to address our aims [30,71]. We believe our sample size of 80 participants (40 intervention subjects and 40 waitlist control subjects) will yield interval estimates of potential intervention efficacy that will be useful for making decisions about next steps (ie, whether to perform more intervention development or launch a larger trial). Power calculations show the planned sample size will produce a 95% CI for mean differences with an expected half-width of 0.45 SD, conveying the precision of preliminary estimates of efficacy.

Data Analysis

Aim 1

Directed content analysis will be used to analyze qualitative data. Directed content analysis is appropriate, as it utilizes a theoretical framework to extend knowledge of data content through a systematic process of coding and identification of categories, themes, and patterns from the interview data [72,73].

Measures of Methodological Rigor

Reliability will be demonstrated by providing a detailed description of the study's purpose, participant sampling, and rationale, as well as the role of the researchers and study team involved [74] and our consistent approach (indicating dependability) to qualitative data collection in aim 1 [75]. Validity will be ensured through member checking [74] of the accuracy and credibility of our findings from the aim 1 interviews. Debriefings will be held after the interviews conclude to determine the validity of our interpretation [74].

Aims 2 and 2a

Data will be analyzed using Statistical Package for Social Sciences (SPSS, IBM Corp). Descriptive statistics will describe participant demographics. To determine whether the intervention is acceptable and feasible, the standard will be an acceptability rating of "good" or "very good," good engagement, and timely completion of study activities in at least 80% of participants. If these standards are met or exceeded, we can conclude that acceptability and feasibility are sufficient for a larger trial. If they are not met, additional formative work on the intervention will be undertaken. CIs for effect sizes will indicate the potential clinical and public health significance and substantiate the need for a larger, more robust clinical trial.

Incomplete or Missing Data

To address the potential for incomplete or missing data while maximizing statistical power and reducing the likelihood of bias, several procedures based on differing assumptions about the random nature of the missing data will be implemented [76]. Missing values may be handled by the full information maximum likelihood method, [77] which works by finding model parameters that maximize the likelihood of each case's observed data [78]. Inverse probability weighting [79,80] and multiple imputation [81-83] will be considered as well. These approaches to handling missing data assume that data are missing at random; that is, missing at random conditionals on values of observed variables. In addition, methods for nonignorable missing data (ie, missing not at random), such as Heckman's selection model [77,84] and pattern-mixture models [81,85,86], will be used. Sensitivity analyses will be used to determine the degree to which results depend on untestable assumptions.

Results

The study is part of a 5-year mentored research development award that received funding from the National Heart, Lung, and Blood Institute on September 1, 2019. The first 2 years of the award were developmental. The remaining 3 years will focus on data collection, analysis, dissemination, and an application for a large-scale follow-up grant. We have published 2 manuscripts formative to this research. The first outlined a framework for using eHealth interventions for chronic illness prevention in sexual-minority men of color [39]. The second manuscript was a scoping review assessing nonpharmacologic behavioral and lifestyle interventions to prevent CVD in persons with HIV [87]. Moreover, aim 1 data collection is 87% complete. We expect to complete all data collection for aim 1 on or before April 30, 2022. Recruitment for aim 2 will begin mid-May 2022.

Discussion

Principal Aims

We will conduct a waitlist randomized controlled feasibility trial of a virtual environment to provide education on CVD prevention to sexual-minority men of color with HIV who are 30 to 65 years old, which to our knowledge has not been done before. We anticipate that using an anonymous virtual environment for prevention education will have great potential to facilitate health-promoting behaviors over the course of the study and thereafter. Strategies for mitigating challenges were created and will be implemented for all aims, as described above. This study has the potential to inform strategies for chronic illness prevention using a virtual environment in underserved and stigmatized communities, which is advantageous, as technology usage as a means of information seeking and education is standard. In a 2011 survey, 83% of adults with a chronic condition reported using the internet to search for health information [88]. According to a Pew Research poll, 98% of adults 30 to 49 years old and 96% of adults 50 to 64 years old are internet users [89]. Moreover, the proportion of adults who have smartphones (and live in households with incomes less than 30 thousand dollars per year) has increased by more than half [90]. This illustrates the changing demographics and reach of technology use in older age groups and in lower socioeconomic status groups. With the evolving advances in eHealth strategies and uptake in use, virtual environments can become a leading tool for chronic illness risk reduction, as 43% of adults 50 years or older are using technology for health and 38% are using it for skill building [91].

Limitations

This study is not without limitations. First, the study is not sufficiently powered to detect intervention efficacy. We are testing the feasibility and acceptability of using a virtual environment. Because of this, generalizability is limited. However, our findings will inform any changes or refinements needed for a larger trial. Second, the use of a virtual environment for CVD prevention education may be daunting for persons who are not avid users of technology and may create a barrier to recruitment. We have tried to mitigate this by creating a frequently asked questions brochure. We will also offer orientation prior to the intervention and technical support as needed. Additionally, prior research on older adults suggests that a large proportion of middle-aged to older adults are now playing online games for entertainment and mental sharpness [92]. Third, recruitment may be slow, due to concerns about privacy and confidentiality in a study focused on CVD prevention in persons with HIV. We will reinforce that the virtual environment is an anonymous online space and that all interactions will be via a user-created avatar who uses a pseudonym.

Conclusion

This study will be the first online virtual environment intervention to address CVD prevention in sexual-minority men of color with HIV. We anticipate that the intervention will be beneficial for CVD prevention education and building peer social supports and will result in changes or modifications in risk behaviors for CVD over time. The ways in which the virtual environment is leveraged can potentially inform strategies on implementation of technology-based behavioral interventions in under-sampled and minoritized communities who are at risk of preventable chronic conditions.

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Conflicts of Interest

Authors CJ and AV are the developers of the Learning in a Virtual Environment (LIVE) platform.

Multimedia Appendix 1

Proposal peer-reviewed summary statement from the National Heart, Lung, and Blood Institute Special Emphasis Panel - K01 Career Development Programs to Promote Diversity in Health Research.

[PDF File (Adobe PDF File), 177 KB - resprot_v11i5e38348_app1.pdf]

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Abbreviations

CVD: cardiovascular disease
LIVE: Learning in a Virtual Environment

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Original Paper

Optimizing an mHealth Intervention to Improve Uptake and Adherence to HIV Pre-exposure Prophylaxis in Young Transgender Women: Protocol for a Multi-Phase Trial

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Abstract

Background: Vulnerable adolescents and emerging adults (aged 18-29 years), particularly young transgender women, are among the fastest-growing HIV positive populations worldwide. Thailand has the highest adult HIV seroprevalence in Asia, with a rate of infection among this population of 18%. Widespread technology offers opportunities for innovative mobile health (mHealth) interventions. Pre-exposure prophylaxis (PrEP) is an efficacious HIV prevention strategy recommended for at-risk individuals. PrEP is highly effective when taken as prescribed, but uptake and adherence have been low, with high discontinuation rates among youth.

Objective: We propose to develop and pilot a multi-component, technology-based intervention to promote PrEP usage. We will adapt an existing 2-session, technology-delivered, motivational interviewing-based intervention to focus on PrEP use in transgender women in Thailand. We call this the Motivational Enhancement System for PrEP Uptake and Adherence (MES-PrEP). We will also refine and enhance YaCool, a mobile app with integrated text messaging developed and used clinically by our Thai team. The new version of the app is called Enhanced YaCool, and it enables self-management of gender and sexual health (including PrEP). Our primary aim is to develop and assess the preliminary efficacy of this mHealth intervention.

Methods: We will utilize a multiphase optimization strategy (MOST) to identify the most effective intervention component or combination of components to improve PrEP usage in Thai transgender women. The study includes two phases: phase I (R21) includes qualitative interviews with key stakeholders to explore barriers and facilitators of PrEP usage through thematic analysis to inform intervention adaptation. Following this, we will adapt and beta-test MES-PrEP and Enhanced YaCool for functionality and feasibility using a community advisory board of HIV-negative Thai transgender women. In phase II (R33), we will conduct a MOST design-based trial to evaluate the feasibility, acceptability, and preliminary efficacy of MES-PrEP and Enhanced YaCool. Eighty HIV-negative participants who are currently taking PrEP and 80 participants who are not will be randomized to four conditions: (1) standard PrEP counseling (the control condition); (2) MES-PrEP and standard PrEP counseling; (3) Enhanced YaCool and standard PrEP counseling; and (4) MES-PrEP, Enhanced YaCool, and standard PrEP counseling. Feasibility and acceptability of the intervention will be assessed through usage patterns and the System Usability Scale. Preliminary impact will be assessed by evaluating the proportion of participants who initiate PrEP and their level of adherence to PrEP. Assessments will

be at baseline and 1, 3, 6, 9, and 12 months postintervention. Biomarkers of adherence to PrEP, HIV, and other sexually transmitted infections will be collected.

Results: Upon project completion, we will have an optimized mHealth intervention to support the use of PrEP by transgender women that will be ready for testing in a larger efficacy trial.

Conclusions: Even though transgender women in Thailand face increasing risks of HIV, few interventions have targeted them. Effective developmentally and culturally tailored interventions are needed to prevent HIV transmission in this high-risk population.

Trial Registration: ClinicalTrials.gov NCT05262426; https://clinicaltrials.gov/ct2/show/NCT05262426

International Registered Report Identifier (IRRID): PRR1-10.2196/37659

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KEYWORDS

transgender women; PrEP; HIV prevention; mHealth; motivational interviewing; Thailand; mobile phone

Introduction

Background

Transgender women are disproportionately affected by HIV globally [1]. HIV prevalence rates among transgender women are 15% to 28% in many countries [2], and higher in young transgender women [3-5]. Young transgender women (aged 18-29 years) are in emerging adulthood, a period marked by increased independence, identity development, and risk-taking [6,7]. Thailand has the highest adult HIV seroprevalence in Asia (1.1% in 2017) [8]. The rate of new HIV infections among Thai transgender women has been increasing in the past decade [9], with a prevalence rate reaching 18% [10]. Transgender women face stigma related to gender identity, limited employment options, and often engage in high-risk behaviors (eg, sex work and substance use) [11-16]. Interventions designed specifically for the needs of this high-risk population are critical to the success of the United Nations AIDS Fast Track Strategy: ending the AIDS epidemic by 2030 [17]. Widespread technology use offers opportunities for innovative mobile health (mHealth) interventions for young people, including transgender women [18-20].

Pre-exposure prophylaxis (PrEP) is highly effective when taken as prescribed, and daily use has been shown to reduce the risk of HIV infection by 92% [21], but PrEP uptake among transgender women worldwide is low. Studies have shown that this is primarily due to lack of awareness, rather than lack of willingness to use PrEP [22,23]. Further, adherence among transgender women has been found to be only 18%, compared to 52% among men who have sex with men [24], yet PrEP research has primarily focused on men who have sex with men [25]. In the Princess PrEP program, the largest PrEP program in Thailand, 232 transgender women began using PrEP in 2019, but only 43 were using it at month 3, reiterating the challenges of adherence among this population [26]. Common facilitators of PrEP uptake among transgender women include a high perception of HIV risk, accurate knowledge of PrEP, and access to support services [27,28]. Barriers to PrEP uptake and adherence include concerns about side effects, especially interactions with gender-affirming hormone therapy, a low perception of HIV risk, the stigma of HIV, health system inaccessibility, exclusion of transgender women from advertising, and lack of research [27-29], especially in low- and middle-income countries. Effective and sustainable behavior-change interventions are needed to promote PrEP uptake and adherence in high-risk populations like transgender women in Thailand and end the global HIV epidemic.

mHealth may offer a powerful tool to promote behavior change, particularly when based on evidence-based interventions, such as motivational interviewing (MI) [30,31]. Mobile apps that offer feedback and self-monitoring of health have been associated with improved health outcomes [32]. There is also evidence that text message reminders can improve adherence to prevention and treatment across many clinical conditions, especially among emerging adults [18,33]. Text messaging and mobile apps may have great potential to promote health self-management and behavior change in young transgender women, but are currently underutilized [7]. Mobile interventions are useful among emerging adults due to nearly universal technology use [34,35], and appear to increase PrEP adherence among young people at risk for HIV [36,37]. Still, very few technology-based interventions have targeted transgender women.

Study Aims

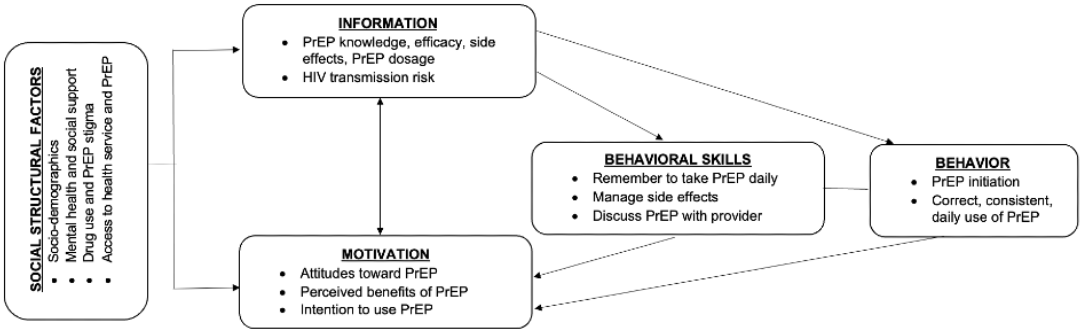
In the proposed study, we will develop 2 potentially synergistic, technology-based, theory-driven interventions aimed at maximizing PrEP usage. We propose to develop and pilot a multi-component, technology-based intervention based on the principles of MI to promote PrEP usage. This process will include 2 guiding frameworks: the ADAPT-ITT (assessment, decision, adaptation, production, topical experts, integration, training, testing) model of intervention adaptation, and a multiphase optimization strategy (MOST) design to identify the most effective culturally and developmentally tailored intervention to address PrEP usage in this population. In phase I (R21), we will adapt an existing 2-session, technology-delivered, MI-based intervention to focus on PrEP uptake and adherence in Thai transgender women who are HIV negative through a systematic, multi-step process [38] to develop what we term the Motivational Enhancement System for PrEP Uptake and Adherence (MES-PrEP). MES-PrEP sessions will be completed on participants' internet-connected mobile devices (eg, smartphones) while at clinics for this study. We will also refine and enhance YaCool, a mobile app with integrated text messaging developed and used clinically by our Thai team. The refined version is called Enhanced YaCool and will enable

self-management of gender and sexual health (including PrEP) in transgender women. These intervention components will be integrated to enhance the impact of a 2-session intervention through daily health self-management. In phase II (R33), we will utilize a MOST framework with a factorial design to efficiently identify the most effective component or combination of components to promote PrEP uptake and adherence in young Thai transgender women. This study may pave the way to scaled-up PrEP implementation, a crucial step in eliminating the HIV epidemic among transgender women in Thailand.

Defining the Theoretical Model of Behavior Change

The information-motivation-behavioral skills (IMB) model and socioecological model (SEM) will serve as conceptual frameworks for the intervention and process of adaptation. Both have been applied to a variety of health promotion topics, including HIV health behaviors [39-41] and PrEP use [42,43]. While IMB includes only individual-level factors, SEM captures individual, structural, and social-level factors. Combining these frameworks may result in a more robust theoretical model. The proposed intervention is primarily focused on behavior change at the individual level, but also addresses structural and social level factors, such as stigma, depression, and access to PrEP. IMB describes behavior change as the result of the joint function of three elements: information about risky behaviors (ie, the risk of not using PrEP) and alternatives (such as using PrEP), the motivation to change behavior, and the behavioral skills to perform the behavior (ie, self-efficacy) (Figure 1). We will develop content to address each of these elements to facilitate PrEP usage among young Thai transgender women.

Figure 1. Integrated application of the information-motivation-behavioral skills model and the socioecological model for uptake and adherence. PrEP: pre-exposure prophylaxis.



The Intervention Components

MES-PrEP Intervention

MES-PrEP is a brief, tailored, 2-session intervention deliverable to any internet-enabled device via the Computerized Intervention Authoring System (version 3.0). A 3D avatar speaks, moves, and displays emotions. At the start of each session, the participant chooses an avatar, who delivers the intervention in a way that closely follows the most recent edition of MI (MI-3) [44]. The avatar evokes importance and confidence (key components of motivation) with MI strategies such as identifying pros of behavior change, providing affirmations to reinforce "change talk" and boost confidence, and identifying strengths and resources. MI strategies are utilized within the motivational enhancement system to promote autonomy, boost self-efficacy, and identify social supports, while also addressing stigma and coping. The intervention manages "counter-change talk" by having the avatar reflect without judgment and provide statements to emphasize autonomy. As with interaction with a human counselor, interactions are synchronous and not reliant on feedback at the completion of the session. Small amounts of education about PrEP are integrated with motivational elements. The intervention is branched, with participants assigned to different branches based on their rating of importance of PrEP and their confidence in taking it; each branch has content tailored to these responses. For example, participants who give a low rating to the importance of PrEP are assigned to a branch that focuses on decisional balance exercises, while those who give a high rating for importance are assigned to a branch that provides reinforcement. The participants are placed in branches that provide content exploring stigma, autonomy, self-efficacy, and social supports. Participants are given feedback on their PrEP knowledge and information on the protective effects of PrEP adherence. Each participant is then asked to set a goal: obtain a PrEP prescription, maintain optimal adherence, practice steps, or think about it more, and asked to identify possible barriers to usage (such as stigma, forgetting, or side effects) and form plans for overcoming these barriers. In the second session (1 month later), participants are assigned to new branches based on whether they met their goal (this branch provides reinforcement and encourages planning for continued success), partially met their goal (this branch focuses on identifying plans for overcoming barriers), or did not meet their goal (this branch reviews the importance of PrEP and encourages confidence in it). The participants may choose a new goal or continue the same goal.

YaCool

YaCool is a mobile app developed by our Thai collaborators to support self-management of gender and sexual health in transgender women. Self-management of health requires skills such as problem-solving, goal-setting, and action planning [45], as well as health behaviors required to effectively remain healthy (eg, adherence to prescriptions and keeping appointments). Self-management assumes autonomy and that emerging adults will increase their responsibility for their own health decisions. YaCool is a passcode-protected app that is installed on users' smartphones and allows users to personalize reminders to take PrEP, record taking PrEP, and calculate adherence. YaCool includes a diary to record sexual activity, the use of preventive

methods, and substance use. It is set up to provide personalized recommendations for PrEP, confirmed by clinic health care staff. YaCool also offers personalized appointment reminders and lab results (eg, testing for sexually transmitted infections [STIs]). We will further refine the content in YaCool and its appearance to allow more seamless integration with MES-PrEP, and will add new features from a list generated during formative work. Our Thai team conducted a focus group with 7 young transgender women. The focus group recommended new features to enhance the YaCool app: (1) lab results to track hormone levels; (2) self-assessment tools (eg, for depression screening); (3) incentives for data input or attendance at clinics; and (4) linkage to mental health providers. In the proposed project, YaCool will be refined and beta tested to develop a new version called Enhanced YaCool to allow transgender women to self-manage gender and sexual health between and after MES-PrEP sessions.

Standard PrEP Counseling (Control Condition)

All study participants will receive one-on-one, face to face counseling focused on sexual and behavioral risk assessment for HIV and other STIs and risk reduction. For those who are at high risk but are not yet ready to start PrEP, the focus will be on risk assessment and perception, awareness of PrEP and postexposure prophylaxis, facilitators of PrEP use, and barriers to access to PrEP. For those on PrEP, the focus will be on adherence. Counseling is standard practice within our partner clinics and will last about 15 to 20 minutes.

Guiding Frameworks

The ADAPT-ITT Model

Development and testing of the interventions (MES-PrEP and YaCool) will be guided by the ADAPT-ITT model [46] for both the R21 and R33 phases. This framework is designed to guide adaptation of evidence-based interventions for people with HIV or at risk of contracting it. It balances rigor with pragmatic concerns (such as cost and time) and has been used, including in our previous work, for interventions targeting diverse populations [38]. ADAPT-ITT begins with a needs assessment and progresses to evaluating the efficacy of the intervention. This is appropriate for this proposal because the need to improve PrEP usage in young Thai transgender women has been established, but specific barriers and facilitators are less clear.

MOST Design

MOST is an efficient, cost-effective, engineering-based approach to identify effective components at the outset of the intervention development process [47,48]. MOST is able to identify active components, in other words, those that make significant contributions to the overall effect. This analytic approach employs factorial designs [49] to identify key combinations for the final phase (confirmation). This study uses MOST to examine the individual and combined effects of MES-PrEP and YaCool on PrEP usage by transgender women.

Methods

Study Setting

Transgender women will be recruited from 2 large clinics in Bangkok, Thailand, for both study phases. Tangerine Community Health Clinic is the first transgender-specific sexual health clinic in Asia and offers gender-affirming, comprehensive, integrated health care. Since 2015, over 3600 transgender clients have received HIV counseling and testing by trained transgender and gender-sensitive health care staff. Rainbow Sky Association of Thailand Clinic is among the first community-based organizations to serve at-risk populations in Thailand. Through funding support by the US Agency for International Development/The US President's Emergency Plan for AIDS Relief and a partnership with the Institute of HIV Research and Innovation, this clinic has implemented the Key Population-Led Health Services Model since 2015. The clinic is located in a densely populated area in Bangkok and provides HIV-related health services for key populations, including transgender women.

Study Design

There are two phases in the study: phase I (R21) and phase II (R33).

Phase IA and Phase IB: Formative Research and Intervention Adaptation (R21)

In phase IA, we will conduct interviews with 20 HIV-negative transgender women (including 10 who are naive to PrEP and 10 who are currently on PrEP; the latter group will include 5 participants with good adherence) and 10 health care providers or community health workers from our partner clinics to explore factors related to PrEP uptake and adherence and guide adaptation of our intervention frameworks to the target population. An interview guide will be created by the investigator team. Based on the IMB model, we will explore three key aspects: (1) information, which explores transgender women's knowledge of PrEP and HIV transmission risk, interest in using PrEP, and the perceived advantages and disadvantages of PrEP; (2) motivation, which includes their attitudes toward PrEP, perception of HIV risk, and reasons for accepting or declining PrEP; and (3) behavioral skills, which examines specific behavioral skills relevant to PrEP initiation and adherence, facilitators and barriers to PrEP initiation and adherence, reasons for keeping scheduled appointments or filling PrEP prescriptions, and reasons for discontinuing or restarting PrEP. We will also explore sources of social support and past successes, as well as strategies and solutions to overcoming barriers. Health care providers will be asked about barriers and facilitators of PrEP and experiences with clients and will be prompted to identify intervention topics related to PrEP. The responses will be used to broadly inform intervention content (eg, what modules to include in the intervention framework), but also more specifically (eg, response options for barriers and sources of social support). We will also prompt the participants for feedback on the content of the intervention (such as by asking them what they would like to know more about PrEP) and delivery (such as by asking how often they would like to receive reminders to take PrEP and what components they would

add to YaCool). Interviews will be audiotaped, transcribed, and translated into English by an independent translator. Interviews will last about 30 minutes. The transgender women and health provider participants will receive $25 for their time.

In phase IB, we will take a motivational enhancement intervention framework that was developed for youth living with HIV in the United States and utilize our results to adapt it to our target population. We will also add features and enhancements to YaCool. The adaptation process will involve two steps: (1) initial programming of the adapted sessions and (2) evaluation of the cultural and developmental acceptability of the intervention content via a community advisory board (CAB) and beta testing by 10 HIV-negative young transgender women. The transgender women will complete 2 MES-PrEP sessions over 1 month. Each session will be videotaped. The transgender women will also download Enhanced YaCool for daily use between and after PrEP sessions. We will administer assessments during beta testing and review the content for cultural and developmental relevancy and MI consistency. During this period, staff will call the participants to check for issues with YaCool. A brief interview will be conducted after beta-testing to (1) identify any technical or other issues with either component, and (2) solicit input on how to improve the delivery and content. Throughout phase IB, we will conduct troubleshooting and revise the programming. Adaptation, production, and refinement will result in the final versions of MES-PrEP and Enhanced YaCool being developed by the end of the R21 phase.

Selection of CAB

CAB members (N=8-10) will be randomly selected from transgender women who complete interviews. Members will meet quarterly (with additional meetings as needed). The primary role of the CAB will be to provide iterative feedback on study materials, recruitment and retention strategies, intervention approaches and content, and disseminating study findings. Operational guidelines will follow best practices for community-participatory research (such as establishing the CAB's function and promoting empowerment). [50] Any inconsistencies in the feedback will be resolved during the meeting, or if necessary, via discussions with the Thai-US team. Detailed notes will be taken during meetings. Study materials will be revised based on CAB feedback. CAB members will receive $25 per meeting.

Phase II: Pilot MOST Design-Based Trial (R33)

We will launch a pilot trial using a full factorial design to evaluate the feasibility, acceptability, and preliminary efficacy of intervention components to increase PrEP uptake and adherence among young Thai transgender women. The trial will examine (1) the effect of each component on participants who are currently on PrEP but not adherent and participants who have not started PrEP and (2) whether the presence or absence of a component has an impact on the performance of other components. While there exist several approaches to construct a MOST trial, we will use a full factorial design given its relative simplicity and cost efficiency [48,51]. For our MOST trial, the 2 intervention components each have 2 levels, resulting in a $2^1 2^1$ full factorial with 4 experimental conditions. MOST requires a well-defined optimization criterion. We will use PrEP uptake and adherence as the measure of success. In order to build an optimized intervention for participants who are on PrEP and participants who are not on PrEP, we will enroll 80 participants who are on PrEP and 80 participants who have not started PrEP. The 80 participants who have not started PrEP will all be individuals who are at high risk and are eligible for PrEP but have not yet decided to start PrEP.

Standard PrEP counseling will be provided to all participants at the beginning of the trial and treated as a constant component in the experiment. After counseling, participants will be randomly assigned to 1 of the 4 experimental conditions (Table 1). Separate randomization for participants who are on PrEP and participants who have not started PrEP will be conducted via Qualtrics (Qualtrics XM). The primary outcome will be PrEP uptake and adherence assessed through computer-assisted self-interviewing (CASI) and dried blood spot (DBS) testing. The main effects of the intervention components and the interactions between them will be estimated using ANOVA. The goal of the R33 phase is to examine intervention strategies based on preliminary effect sizes, feasibility, and acceptability and prepare for a fully powered randomized controlled trial to evaluate the optimized intervention package.

Table 1. Study experimental conditions.

Experimental condition (n=20 for each condition)	Standard PrEP[a] counseling	Motivational enhancement system for PrEP	Enhanced YaCool
1	Yes	Yes	Yes
2	Yes	Yes	No
3	Yes	No	Yes
4	Yes	No	No

[a]PrEP: pre-exposure prophylaxis.

Study Sample

Eligibility criteria, screening, and consent are the same for the R21 and R33 phases. All participants will be transgender women who are eligible based upon inclusion criteria consistent with US Centers for Disease Control and Prevention and Thailand Ministry of Public Health PrEP guidelines [52,53]: (1) age 18 to 29 years; (2) male sex at birth; (3) self-identification as a woman or transgender woman or cultural identification with the female spectrum; (4) laboratory-confirmed HIV negative status; (4) self-reported recent history of condomless sex; (5) ability to understand, read, and speak Thai; and (6) either no existing use of PrEP (group 1, PrEP naive) or currently on PrEP but not adherent (taking ≤3 pills/week) in the past month (group

2, PrEP users). The exclusion criteria are (1) a serious cognitive or psychiatric problem compromising the ability to provide informed consent; (2) active suicidal ideation or major mental illness (eg, untreated psychosis or mania) at the time of the interview (these patients will be referred for treatment); (3) laboratory or clinical findings that would preclude PrEP initiation (eg, decreased creatinine clearance); and (4) current enrollment in another HIV intervention study. We will recruit transgender women from a broad range of socioeconomic backgrounds; therefore, mobile phone ownership is not required for participation, and a mobile phone will be provided at no cost to participants who do not have one.

Sample Size of Trial

Using G*power 3.1.9 (Heinrich-Heine-Universität Düsseldorf) for the ANOVA, we will set the effect size *F* at 0.35, α at .05 and the sample size at 80 (20 for each experimental condition). The calculated statistical power is 80% for detecting the 2 main effects, MES-PrEP and YaCool, and 73% for detecting their interaction. The pilot trial is not an efficacy study, and therefore is not fully powered to detect both main effects and interactions, but has a sample large enough to detect a medium to large effect size for MES-PrEP and YaCool.

Recruitment and Enrollment Procedures

Recruitment will be led by a Thai transgender woman researcher with 5 years of experience developing materials and recruiting young transgender women for HIV prevention research. Materials will be placed at physical and online venues, including study clinical sites and community venues that serve transgender women (eg, health centers, bars and clubs, and community organizations). Participants will also be recruited by paid study recruiters who identify as transgender women using direct outreach in the community. These efforts have been successful in other projects seeking to enroll transgender women [26,54,55], and as such, we do not anticipate having problems reaching our target sample.

Potential participants will complete a prescreener over the phone or in person. If eligible and interested in participating, the transgender women will complete an in-person screening at one of the study clinics. After providing verbal consent, they will complete a prebaseline survey assessing basic demographic information, history of HIV and STIs, HIV testing, access to HIV and STI diagnostic and treatment services, recent sexual behavior, use of PrEP, and knowledge and acceptance of PrEP. They will undergo HIV testing (with a fourth-generation serum) and screening for hepatitis B (with surface antigens and antibodies), hepatitis C (with antibodies), and renal insufficiency (with serum creatinine testing) to confirm their eligibility for PrEP and the study. Research staff will determine if the transgender women meet the inclusion criteria and have completed informed consent. The screening visit, enrollment, and baseline assessment should occur on the same day, or failing that, within one week. After signed consent is obtained, participants will be asked to provide contact information for a family member or friend who can be called if they cannot be reached.

Data Collection Tools and Procedures

Self-report measures will be administered using the cloud-based CASI system in Thai at baseline, immediately postintervention at the end of the first month, and at 3, 6, 9 and 12 months. In CASI, the participant sees each question and a list of responses on a private iPad screen. The response is entered by pressing a number keypad. The data are stored directly in the password-protected Qualtrics system. CASI elicits more valid and reliable data than face-to-face or written questionnaires [56-58]. The topics we assess are sensitive; CASI allows greater privacy for honest responses [59,60] and reduces missing data and interviewer bias. Our team has been using Qualtrics for CASI for over 8 years.

The primary acceptability outcome will be measured by the System Usability Scale, a 10-item Likert scale giving an overall view of subjective assessments of usability. The System Usability Scale is technology agnostic and provides a global measure of system satisfaction [61]. A score of >50 (out of 100) indicates that an intervention is acceptable [62]. We will also assess interest in future use at study completion. For feasibility, we will assess the number of responses and frequency of usage of Enhanced YaCool, the number of MES-PrEP sessions completed, cumulative time spent in MES-PrEP, and recruitment rates. PrEP uptake will be assessed using self-reported measures (from participants who left the clinic with an emtricitabine/tenofovir disoproxil fumarate [TDF/FTC] prescription), confirmed via chart review and pharmacy records. Adherence to PrEP will be measured using (1) a young adult adherence interview with a visual analog scale [63]; (2) a 4-week percentage taken measure (answering the question “What percentage of the time were you able to take all your PrEP medications in the past 4 weeks?”) [64]; and (3) biological testing using a DBS report on 80% TDF/FTC adherence after at least 3 weeks of regular adherence. The results of DBS testing will be triangulated with the self-reports. We will assess IMB model constructs—knowledge, attitudes, motivations, and behavioral skills related to taking PrEP, and important contextual factors (age, education, depression, and PrEP-related stigma).

Data Analysis

Intervention Evaluation

We will estimate retention rates, overall and per condition, and examine differences across conditions using the chi-square test. We will assess differences in acceptability using the *t* test or the Mann-Whitney test. The minimum criteria for acceptability and feasibility will be point estimate for mean System Usability Scale score ≥50 and having at least 50% of participants respond to YaCool at least once and complete at least one MES-PrEP session [62]. Using a $2^1 2^1$ full factorial design, we will test the main effects and interactions between components with an ANOVA using effect coding (1 = “no” condition; +1 = “yes” condition) rather than dummy coding (ie, 0, 1). A participant will be classified as adherent if her tenofovir level in DBS reflects the use of TDF/FTC tablets 4 to 7 days a week over the prior 6 weeks (a level with an almost 100% preventive effect). Participants whose tenofovir levels cannot be assessed will be classified as nonadherent. The intervention effect on PrEP uptake and adherence will be further assessed using

mixed-effects modeling controlling for potential confounding factors (eg, age and education) and possible baseline differences. Missing data will be handled using full information maximum likelihood estimation. Effect sizes will be estimated for the primary outcomes. All analyses will be conducted using the SAS 9.4 statistical software package (SAS Institute Inc).

Structural equation modeling will be used to examine the extent to which the targeted variables (eg, information, motivation, and self-efficacy) mediate the intervention effect. Guided by our conceptual model, we will assess the effects of intervention on the mediator and the effects of the mediator on the outcome, controlling for other mediators and confounders, and we will then estimate the proportion of the intervention effect explained. Mediation models will be tested using MPlus (Muthén & Muthén). Given the limited sample size, conclusions from the mediation analyses will be limited and treated with caution, but modeling will allow us to explore the constructs of IMB and potential predictors in preparation for a larger efficacy trial.

Component Selection

We will make a preliminary selection of components that have achieved main effects (ie, that exceed statistical significance or have a medium to large effect size). This selection will be reevaluated if we find any substantial interaction effects and understand how the components work in combination. Optimization criteria (ie, PrEP uptake and adherence) will then be combined with other information (eg, cost, feasibility, and scalability) to make the final component selection [65]. This information will guide assembly of an optimized intervention package that achieves the target outcomes with the least resource consumption and participant burden.

Ethics Approval

The research protocol and methodology were reviewed and approved by the by the University of Massachusetts Chan Medical School Human Investigation Committee and the Research Ethics Review Committee of Chulalongkorn University in Thailand (H00023527). The trial has been registered at Clinicaltrials.gov (NCT05262426).

Results

Recruitment for this study began December 2021 for phase I. Qualitative interviews were completed with 28 transgender women in February, 2022. Analyses are ongoing. Results will be disseminated to key stakeholders and used to inform intervention adaptation and refinement. Phase II, the pilot feasibility and acceptability trial, will begin in August 2023 following approval from the National Institutes of Health to begin the next phase. The findings will be disseminated to stakeholders and communities of interest using peer-reviewed journals, academic conferences, and other communication channels.

Transition Milestones

The major goal of the R21 phase is to develop MES-PrEP and Enhanced YaCool and to establish the initial feasibility of this mHealth intervention. Formative research will inform development and refinement, followed by adaptation and production of the mHealth intervention. The final step of ADAPT-ITT is testing, which will include a small pilot feasibility testing study with 10 participants (the R21 phase), and a randomized controlled trial of the mHealth intervention (the R33 phase). We will also develop optimized research protocols for a large efficacy trial.

Discussion

Principal Aims

The main aim of this study is to develop an optimized, culturally tailored, mobile intervention to improve PrEP uptake and adherence among transgender women in Thailand. Transgender women are among the most at-risk groups for HIV transmission, yet PrEP usage has remained low. We propose to adapt 2 existing intervention components for this target population using input from key stakeholders within our participant population. Using an mHealth approach, we will test different combinations of our intervention components to assess which combination results in the best outcomes in terms of feasibility, acceptability, and signals of intervention efficacy. Based on our theoretical models of behavior change (IMB and SEM), we anticipate that the combination of all 3 intervention components (MES-PrEP, YaCool, and standard PrEP counseling) will be found to be the optimal intervention condition, but this is yet to be determined. If successful, this study will be among the first to identify an optimized intervention package for transgender women in Thailand toward improving PrEP usage and ending the HIV epidemic globally. It may also be more sustainable than traditional in-person approaches to behavioral intervention because of the use of relatively low-cost and widely available mobile technologies.

Planned Next Steps

The project will be conducted to develop an optimized technology-based intervention for HIV-negative young Thai transgender women and prepare for a future large-scale randomized controlled trial. For a fully-powered R01 project, we propose a multisite study testing the efficacy of mobile MES-PrEP and Enhanced YaCool using a type 2 effectiveness-implementation design [66] with testing of intervention effectiveness in eliciting the desired outcomes across the PrEP cascade and gathering of information on the implementation of technology-based intervention, including cost analysis to assess the relative cost of implementing the intervention.

Limitations

Retention and differential loss to follow up are threats to internal validity. Possible barriers are no-shows at clinic visits or refusal to participate. Techniques we will use to increase compliance with appointments include advanced scheduling, reminders between visits and prior to follow-up surveys, texts, emails, and compensation for time spent. If a participant misses a follow-up survey or intervention session, additional outreach will be made to support engagement. Threats to internal validity of the study may also arise if there is insufficient attention to quality assurance during data collection and intervention delivery. Possible technological difficulties with the software, text

messaging, and server are another concern. However, we have experience across multiple projects using these technologies and troubleshooting and tracking any issues, and technical assistance and software programming are written into the budget.

Conclusions

This study addresses a critical problem (high HIV incidence and low PrEP use) among an at-risk population (transgender women). We are developing 2 potentially synergistic, technology-based, theory-driven interventions aimed at maximizing PrEP usage. Thailand was part of the world's first PrEP trial (iPrEP) and several PrEP demonstration projects, yet uptake and adherence remain low. Our study is timely and relevant as it addresses major challenges related to PrEP use. It is responsive to the US Preventive Services Task Force's recommendations calling on research to increase PrEP uptake and adherence [67]. This study may pave the way to scaled-up PrEP implementation, a crucial step in eliminating the HIV epidemic among transgender women in Thailand.

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Authors' Contributions

KKM and BW wrote the manuscript and designed the study protocol. NP, RJ and PS created the YaCool app. KKM, BW, NP, RJ, CR and SN are designing intervention content. RJ and PS led stakeholder engagement and led focus groups. All authors provided input for the protocol design and reviewed the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ADAPT-ITT: assessment, decision, adaptation, production, topical experts, integration, training, testing
IMB: information-motivation-behavioral skills model
MES-PrEP: Motivational Enhancement System for Pre-Exposure Prophylaxis
MI: motivational interviewing
MOST: multiphase optimization strategy
PrEP: pre-exposure prophylaxis
SEM: socioecological model
STI: sexually transmitted infection

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