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Protocol

Food Allergy Symptom Self-Management With Technology (FASST) mHealth Intervention to Address Psychosocial Outcomes in Caregivers of Children With Newly Diagnosed Food Allergy: Protocol for a Pilot Randomized Controlled Trial

Brantlee Broome^{1*}, PhD, MSN, RN; Mohan Madiseti^{1*}, MSc; Margaret Prentice^{1*}, MBA; Kelli Wong Williams^{2*}, MD, MPH; Teresa Kelechi^{1*}, PhD, RN

¹College of Nursing, Medical University of South Carolina, Charleston, SC, United States

²College of Medicine, Medical University of South Carolina, Charleston, SC, United States

* all authors contributed equally

Corresponding Author:

Brantlee Broome, PhD, MSN, RN

College of Nursing

Medical University of South Carolina

99 Jonathan Lucas Street

Charleston, SC, 29425

United States

Phone: 1 843 792 3370

Email: broomeb@musc.edu

Abstract

Background: Approximately 2.4 million children in the United States suffer from food-induced anaphylaxis, a condition that is annually responsible for over 200 deaths and 200,000 emergency room visits. As a result, caregivers of children newly diagnosed with severe and life-threatening food allergic reactions experience clinically significant symptoms of psychological distress, including fatigue, anxiety, depressed mood, social isolation, and substantially reduced quality of life. Despite this recognition, there is a lack of caregiver-centered self-management interventions to address these concerns.

Objective: In this protocol, we propose to develop and conduct feasibility testing of a technology-enhanced, self-management, mobile health, smartphone app intervention called Food Allergy Symptom Self-Management with Technology for Caregivers (FASST) designed to meet the psychosocial health needs of caregivers of children with a new diagnosis of food allergy.

Methods: This pilot study uses qualitative work (Phase I) to inform a 4-week longitudinal randomized controlled trial (Phase II). In Phase I, 10 caregivers of children (≤ 18 years old) with established food allergy (≥ 1 year from diagnosis) will participate in semistructured interviews to inform the development of the FASST app. In Phase II, 30 caregivers of children (≤ 18 years old) with a newly diagnosed food allergy (≤ 90 days from diagnosis) will be randomized 2:1 to receive the FASST intervention ($n=20$) or control condition (basic app with educational resources; $n=10$). Process measures include feasibility, caregiver acceptability, adherence, and satisfaction. Outcome measures include caregiver fatigue, anxiety, depression, sleep, self-efficacy, and quality of life measured at baseline, week 4, and 3 months post study completion.

Results: Phase I study activities have been completed, and Phase II participant enrollment into the randomized controlled trial is expected to commence in 2021.

Conclusions: With limited readily available resources at their disposal, the results from this study have the potential to provide caregivers of children with a newly diagnosed food allergy a tool to help them self-manage and mitigate negative psychosocial factors during a critical time period in the caregiving/condition trajectory.

Trial Registration: ClinicalTrials.gov Identifier NCT04512924: <https://clinicaltrials.gov/ct2/show/NCT04512924>

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KEYWORDS

caregiver well-being; food allergy; self-management; mhealth, randomizes mixed trial; caregiver; well-being; emergency room; smartphone app; smartphone; children

Introduction

In the United States, approximately 6 million children suffer from food allergies (FAs) [1], a major public health concern as its prevalence has continued to increase over the past 2 decades [2]. Food-induced anaphylaxis (FIA) is an associated health risk affecting more than 40% of children diagnosed with FA [2]. Although FIA reactions in children are rare, they are responsible for over 200 deaths and 200,000 emergency room visits annually in the United States [3]. There is no cure for FA, and standard of care is strict avoidance of implicated food allergens and emergency medical treatment of symptoms after exposure [3]. There are many challenges to a caregiver's ability to adhere to this standard of care—most notable is the potential for a fatal reaction from ingestion of food substances that are often invisible due to cross-contact with contaminated surfaces or the presence of unidentifiable food ingredients within processed foods. This can create an ever-present and heightened state of vigilance, anxiety, and stress-related fatigue as caregivers learn to both manage FA as a chronic condition and respond to food-induced reactions as an acute illness or event. Caregivers of children with newly diagnosed FA experience significant life behavior alterations that can test their ability to balance appropriate vigilance and management strategies while tempering the effects on quality of life [4].

Background

The principal investigator's (PI's) research, and that of others, highlights that caregivers of children with FA describe the physical challenges of care as overwhelming and constant. The perpetual hypervigilance and ensuing exhaustion associated with time-consuming and persistent condition-management activities—such as monitoring a child's food consumption at school or when with friends and when shopping for and preparing special food—have a significant impact on caregiver quality of life and are associated with fatigue, uncertainty, constant stress, social isolation, reduced spontaneity, and persistent anxiety, fear, and depression [5-12]. Following diagnosis, caregivers experience a period of psychosocial adjustment where these symptoms are most pronounced [13]. As caregivers begin to understand the necessary precautions and potential consequences of accidental ingestion associated with FIA and the required condition management activities, fear and anxiety emerge as predominant emotions. While a certain level of anxiety is essential for adequate management, high levels of sustained anxiety in caregivers of children with FA can be maladaptive, increasing the overall burden of caring for a child with FIA and negatively impacting the caregiver's ability to provide care to self, child, and family [14]. Symptom self-management is exceedingly relevant to the caregiver of a child with newly diagnosed FA(s) as condition management is complex and compounded by factors outside of the caregiver's control and is further intensified by the lack of definitive treatment or cure.

Our recent preliminary research [5] corroborates findings in the literature [6-14], suggesting that 32% of caregivers with a child who is newly diagnosed with FA(s) experience clinically significant psychological distress [15]. Despite recognition that family caregivers of children with severe FAs experience these adverse psychosocial symptoms and decreased quality of life, there are a lack of caregiver-centered self-management interventions to address their symptoms. The lack of self-management interventions may lead to persistence of these distressing symptoms, possibly beyond the period of initial diagnosis.

In this protocol, we propose a 2-phase pilot study to develop a mobile health (mHealth) smartphone app intervention called Food Allergy Symptom Self-Management with Technology for Caregivers (FASST) that specifically addresses psychosocial symptoms experienced by caregivers of children with newly diagnosed FA by providing targeted education and the ability to self-monitor and self-manage experienced symptoms. In Phase I of the study, we will conduct key informant interviews and collect data from caregivers of children (≤ 18 years old) with established FA (diagnosed with FA ≥ 1 year ago) to guide the development process for the FASST app. We consider these caregiver interviewees as co-designers of our intervention as they possess a level of experience and understanding of FA management and the psychosocial consequences of caring for a child during the critical period following a child's initial FA diagnosis that caregivers of newly diagnosed children do not. In Phase II, and over the course of 6 months, we will conduct preliminary feasibility testing of the FASST app in a 4-week longitudinal, pilot, randomized controlled trial of 30 caregivers of children ≤ 18 years of age who are newly diagnosed (≤ 90 days from diagnosis) with FA(s).

Aims

Using qualitative Phase I work, the primary aim of the main study (Phase II) is to conduct preliminary testing of implementation processes including feasibility, acceptability, adherence, and satisfaction (using the RE-AIM [Reach, Effectiveness, Adoption, Implementation, and Maintenance] framework with process measures, surveys, and key informant interviews) among 30 caregivers randomized to use FASST ($n=20$) or the control condition (ie, basic app with resource links; $n=10$) over 4 weeks. The secondary aim of this phase is to obtain estimates of variability and measure caregiver outcomes including fatigue, anxiety, depression, sleep, self-efficacy, and quality of life at baseline, 4-week intervention completion, and 3 months postintervention.

Methods

Phase I

Using a purposive sampling strategy and qualitative descriptive approach, we will identify, recruit, and conduct semistructured key informant interviews with 10 caregivers of children (≤ 18

years old) with established (≥ 1 year from diagnosis) FA(s). The purpose of these interviews is to elicit feedback from caregivers that are familiar with the disease and management processes. Caregivers will be informed prior to conducting interviews that their feedback will be used to inform both the content and design elements of FASST as well as the overall utility of the app.

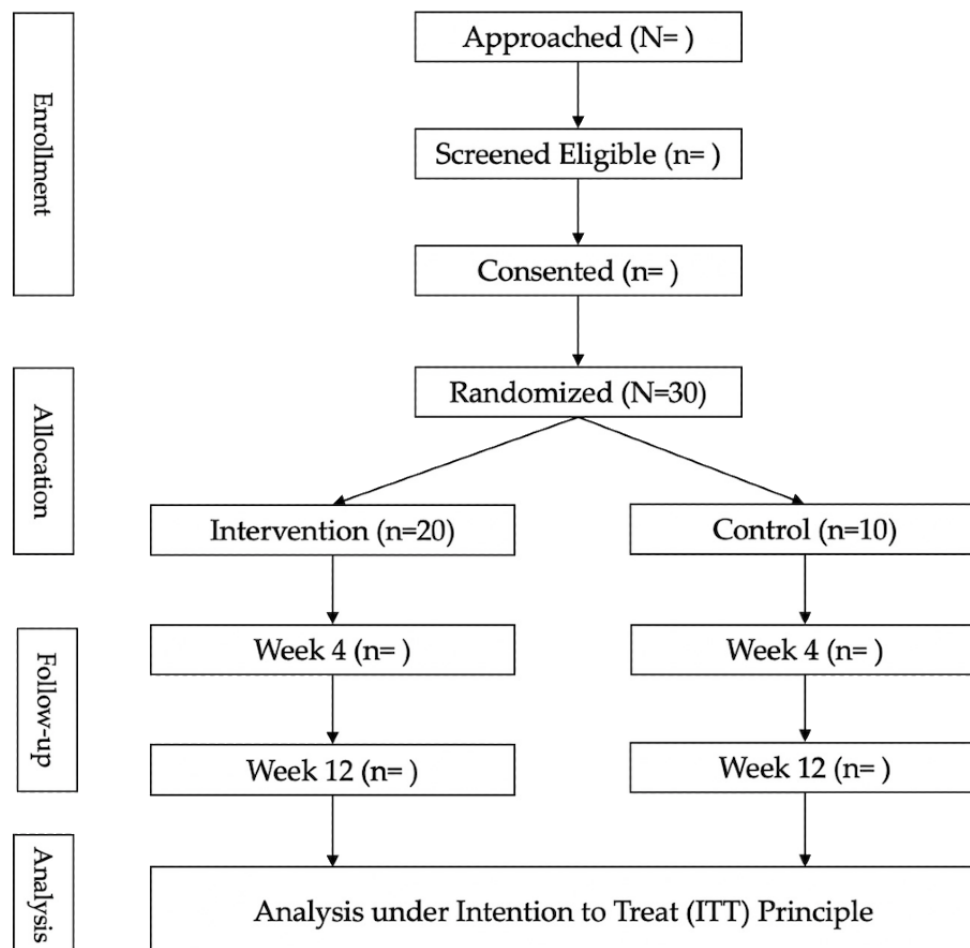
Prior to conducting the interviews, participants will be asked to download and review 2 different free and commercially available smartphone mobile apps: one related to FA management and another related to general lifestyle stress management. Participants will be asked to review both apps for a period of 7-10 days, noting specific elements (content and function) of each app that they would have found helpful during their child's initial period of FA diagnosis. After 7-10 days, the researchers will schedule one-on-one interviews and ask 8-10 open-ended questions with probes using an interview guide. Questions for the interview will be based on an interview guide; however, flexibility will be afforded to expand upon and probe individual responses. Participants will be asked about their

personal experience in the first year of managing their child's FA, with close questioning regarding the first 4 weeks of management and the perceived impact on their psychosocial well-being and overall quality of life, and to provide user feedback on the acceptability, feasibility, and usability of the 2 mobile apps for the management of FAs and in reducing caregiver burden. Following data analysis, results from the Phase I interviews will be used to inform the design of an mHealth smartphone app (FASST) to meet the specific needs of caregivers of children 18 years of age or younger with a newly diagnosed FA(s) (≤ 90 days from diagnosis). Caregivers participating in Phase I will receive a US \$50 gift card upon study completion.

Phase II

The methodology for the Phase II clinical trial follows the directives proposed in the CONSORT (Consolidated Standards of Reporting Trials) 2010 Statement: Extension to randomized pilot and feasibility trials [16]. The overall flow of the Phase II trial is outlined in Figure 1.

Figure 1. Phase II: CONSORT (Consolidated Standards of Reporting Trials) diagram of participant flow through the study.



Design, Setting, and Participants

We designed a longitudinal, randomized controlled trial with 3 study visits (baseline, week 4, and week 16) over a 4-month study period. Study participants will be recruited from an Allergy and Immunology clinic at a large tertiary care academic medical center in South Carolina. Participants from all racial

and ethnic backgrounds will be approached and invited to volunteer as research participants. For inclusion in this phase, caregivers must have a child ≤ 18 years of age who is newly diagnosed (≤ 90 days from diagnosis) with FA(s). Exclusion criteria include (1) caregivers who carry a diagnosis of cognitive impairment or deficit or an observed lack of understanding of the study demands during the informed consent process and (2)

inability to speak or read English. To assess cognitive impairment, when determining eligibility, study personnel will ask potential participants, "Have you been diagnosed by a health care provider with a cognitive impairment or memory disorder?" If the potential participant answers, "yes," they will not be consented for participation in the study. Eligible and enrolled participants will receive a US \$50 gift card for study compensation at each of the 3 data collection points, with participants in key informant interviews (postintervention) receiving an additional US \$50 gift card. Study endpoints include successful study completion, participant consent withdrawal, and PI termination due to failure to adhere to the protocol, loss of contact with the participant, or unexpected adverse events.

Sample Size

We will recruit 30 caregivers to participate in the intervention phase of the study. Because this is a pilot study and will not be testing hypotheses or proposing use of inferential statistics, a target sample size of 30 is appropriate [17].

Randomization and Blinding

We will allocate 20 participants to the study intervention arm and 10 participants to the control arm. The allocation sequence to the 2 groups will be determined using a 2:1 block randomization scheme generated by computer and developed by the study biostatistician. The PI and biostatistician will be blinded to allocation.

Intervention

The FASST mHealth intervention will be a multicomponent (3-part) technology-based package delivered via a mobile device and used over the 4-week study period. The intervention will target influences and processes informed by the Individual and Family Self-management Theory [18].

Component 1 (education and support) will consist of continuous access to directed educational resources about FA and its management. These materials will be easily accessible via a mobile device and will include embedded PDFs and links to websites developed and tested by authoritative sources. An example includes education materials provided by Food Allergy Education and Research (FARE), the leading national organization and most trusted source of FA information, programs, and resources, such as the Food Allergy & Anaphylaxis Emergency Care Plan. To address potential literacy barriers, all resources will be provided in a web-compatible format and compliant with current accessibility guidelines.

Component 2 (symptom monitoring and tracking) will consist of a daily symptom log function for tracking overall well-being as well as daily activity; sleep; and psychosocial, emotional, and physical symptoms. All logged symptoms will be uploaded to a portal for assessment by study personnel. The PI or research assistant (RA) will send a daily text reminder to participants randomized to the intervention arm of the study reminding them to complete their daily symptom, activity, and sleep log. Logged symptom trends will be graphically illustrated by the app for participant viewing. Based on feedback from component 2, participants will be given directed guidance, as described in the

following paragraphs, related to component 3 (symptom self-management).

Component 3 will consist of symptom-based interventions participants can utilize in real time. For example, if a participant logs symptoms related to anxiety, the app will recommend a brief guided intervention for relaxation, such as meditation or deep breathing. If a participant logs symptoms related to fatigue, the app will recommend the participant listen to a short audio clip that offers ideas for achieving better sleep or suggestions for good sleep hygiene. We will collect data via the app on the frequency and patterns of usage and will also collect measure data at baseline, 4-week intervention completion, and 3 months postintervention. In addition, the RA will send caregivers a weekly text message using a semistructured message script to "check in" with participants and promote engagement.

Controls

Participants randomized to the control arm will only receive the caregiver education and support materials (component 1) of the FASST app. All other caregiver baseline and outcome measures will be collected as scheduled by study personnel.

Study Procedures

Once consented, participants will be randomized and asked to download the FASST app from the Apple App Store onto their mobile device. Participants randomized to the intervention arm will receive components 1, 2, and 3. Those randomized to the control arm will only receive component 1. The PI or RA will deliver detailed verbal instructions to the participants in both arms of the study on the use of the app and the respective intervention components. Participants will also receive written instructions and a contact number for technical assistance if needed. Baseline measures will be collected during the same meeting. Participants will participate in the intervention over a 4-week period. At the end of the 4-week period, the PI will conduct a postintervention interview via telephone with each individual caregiver participant. The PI will also collect frequency and patterns of usage data from the app portal at 3 months postintervention to assess implementation and preliminary evidence of maintenance. The PI will meet with the RA weekly during the intervention.

Postintervention Key Informant Interviews

We will randomly select 5 participants from each study arm in Phase II and ask them to participate in postintervention key informant interviews with the PI to obtain more in-depth data on accessibility, usability, and adherence to intervention. Semistructured interviews will be conducted via phone using a qualitative descriptive approach [19] and will last approximately 30-60 minutes. Questions for the interview will be based on an interview guide; however, the interviewer will allow flexibility with the interview such that subsequent questions may be modified based on participant responses. Participant qualitative interviews will be audio recorded, transcribed, analyzed with directed content analysis, and interpreted to evaluate the feedback.

Data Collection and Measures

Participants will complete a basic demographic questionnaire at baseline and self-reported measures at baseline, 4-week intervention completion, and 3 months postintervention.

Participants will complete the questionnaire and measures using their personal mobile device or computer. The SPIRIT diagram (Figure 2) summarizes the schedule of enrollment, interventions, and assessments across the study.

Figure 2. Study SPIRIT diagram. FASST: Food Allergy Symptom Self-Management with Technology for Caregivers; PROMIS: Patient-Reported Outcomes Measurement Information System.

TIMEPOINT	STUDY PERIOD			
	ENROLLMENT	ALLOCATION	POSTALLOCATION	
	Day -1	Day 0	Week 4	Week 16
ENROLLMENT				
Eligibility screening checklist	X			
Informed consent	X			
Allocation (2:1 randomization)	X	X		
INTERVENTIONS				
FASST (Intervention)		X	X	X
Enhanced Usual Care (Control)		X	X	X
ASSESSMENTS AND MEASURES				
Demographics and characteristics		X		
PROMIS Fatigue		X	X	X
PROMIS Depression		X	X	X
PROMIS Anxiety		X	X	X
PROMIS Sleep Disturbance		X	X	X
Food Allergy Quality of Life - Parental Burden (FAQoL-PB)		X	X	X
Food Allergy Self Efficacy Scale for Parents (FASE)		X	X	X
Impact of COVID-19 on Food Allergy Management (ICFAM)		X	X	X
Semistructured end-of-study interview				X

Data Management

This study will use Research Electronic Data Capture (REDCap) for e-consenting, data capture, and data management. REDCap is a software toolset and workflow methodology for the electronic collection and management of research and clinical trials data. REDCap provides secure, web-based, flexible applications, including real-time validation rules with automated data type and range checks at the time of data entry. Exports are made available for several statistical packages including SPSS, SAS, SATA, R, and Microsoft Excel.

Data Analysis

We will collect data from multiple measures informed by the RE-AIM framework to assess feasibility and inform future efficacy and effectiveness trials. Variables will include those pertaining to the study procedures and processes as well as participant demographic and clinical variables. Specifically, 95% confidence intervals for proportions will be used to estimate dichotomous outcomes including the proportion of caregivers who agree to participate out of the number approached and proportions providing daily symptom monitoring or tracking, using the education component, etc. For the continuous feasibility measures (patient satisfaction scores from patient surveys and end-of-study interview), frequency distributions and the median and mean responses (with 95% confidence intervals) will be obtained.

Demographic and clinical variables obtained at baseline will be described via measures of central tendency (mean, median), variability, and frequency distributions, as appropriate. In addition, demographic and clinical characteristics for those who completed the study protocol versus those who did not complete the study protocol will be compared to better describe the population for this study. For continuous measures for the

caregiver (fatigue, anxiety, depression, quality of life, sleep disturbance, and self-efficacy), the difference between pre- and postintervention measurements will be estimated via 95% confidence intervals.

Data collected from postintervention key informant interviews will be analyzed using directed content analysis [20] and nVivo qualitative data analysis software version 12 [21]. Consistent with the directed content analysis approach, initial coding categories will be identified according to the guiding theoretical model and for this study, will reflect the RE-AIM domains.

Data Safety and Monitoring

This study employs the use of a National Institutes of Health (NIH)/National Institute of Nursing Research (NINR) Scientific Review Group–approved Data and Safety Monitoring Plan. The Data and Safety Monitoring Plan utilizes a Safety Monitoring Committee comprised of an independent nurse practitioner (registered nurse, PhD), the study biostatistician (PhD), and the trial director (MS). After the initial participant study enrollment, the Safety Monitoring Committee is set to convene semiannually to review all adverse events, monitor the study safety profile, and make recommendations regarding study modification, termination, and continuance.

Ethical Considerations

The study was approved by an institutional review board, conforms to the Declaration of Helsinki, and will be conducted in compliance with Good Clinical Practices of the International Conference of Harmonization. Parental caregivers provide written informed consent for their study participation. The study was registered on 08/14/2020 in ClinicalTrials.gov (NCT04512924).

Resource Sharing

Data collected from the PROMIS (Patient-Reported Outcomes Measurement Information System) measures will be entered for resource sharing through the Biomedical Research Informatics Computing System at the NINR. The data obtained in the current study will be available from the PI upon reasonable request after publication of the results on the main research questions. Results will be shared with study participants and made publicly available in compliance with NIH Open Access Policy.

Results

Progress to Date

All Phase I study activities have now been completed. Based upon this work, we are presently working with our software development team to make final refinements to the FASST app prior to Phase II implementation. In conjunction with our software development team, the app is being developed for the iOS platform. Sample smartphone screen images from the mHealth app are provided for illustrative purposes in [Figures 3 and 4](#). Phase II study enrollment is expected to commence in 2021.

Figure 3. Sample Food Allergy Symptom Self-Management with Technology for Caregivers (FASST) mobile health (mHealth) smartphone app screen image.

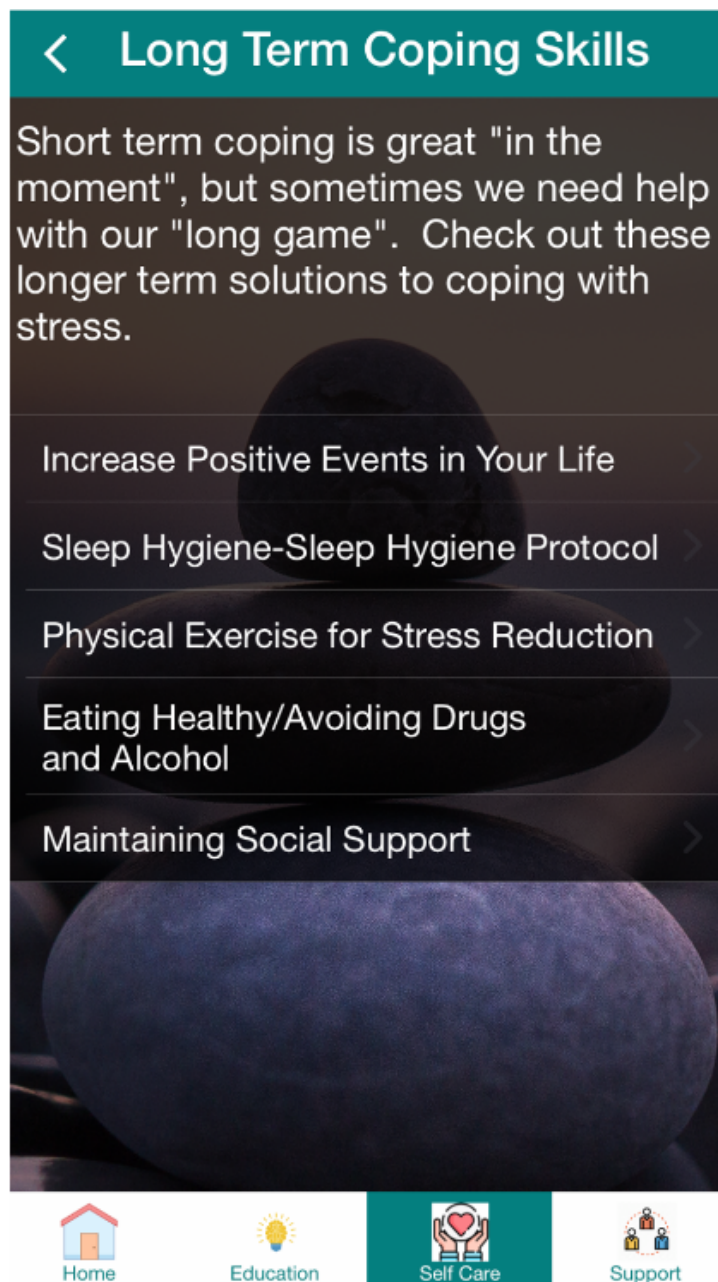
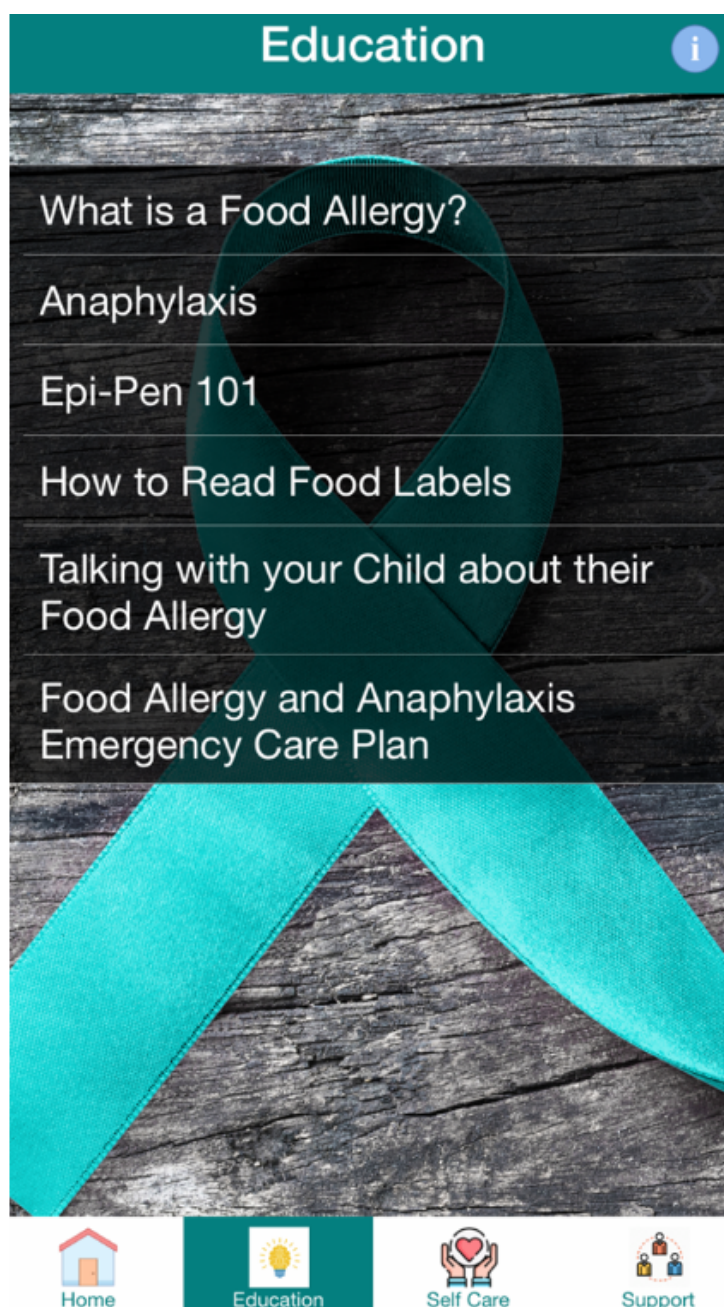


Figure 4. Sample Food Allergy Symptom Self-Management with Technology for Caregivers (FASST) mobile health (mHealth) smartphone app screen image.



Lessons Learned

During the formative Phase I part of this study, multiple lessons were learned, mainly pertaining to needed operational and procedural changes so as to ensure the continuity of human subject research during the COVID-19 pandemic.

Recruitment for Phase I began in late April 2020, just as community and institutional social and physical distancing restrictions related to COVID-19 were mandated, and as such, the original protocol was modified through an amendment to allow for completion of all study procedures remotely (eg, participant interviews conducted via phone instead of face-to-face and study compensation mailed to participant home address rather than in person). All phone interviews were successfully audio-recorded and transcribed for analysis; however, this mode of contact with participants limited capture

of nonverbal cues that may have led to further probing. Another Phase I challenge involved postponed development of the FASST mobile app. Our technology development team was presented with higher priority institutional demands in response to COVID-19. As such, progress on app development experienced significant delays.

While COVID-19 has presented several challenges to the study, we believe it also has resulted in some unintended consequences that benefited the timely completion of Phase I study activities. During this phase, 11 potentially eligible participants were identified through their electronic health records and approached by the researchers regarding study interest and participation. All participants (11/11) responded within 24-48 hours of initial contact and verbally expressed both an interest and a willingness to participate in Phase I. Of these interested participants, 91%

(10/11) were screened eligible, and 100% (10/10) successfully completed all Phase I activities. We hypothesize these observed high rates were possibly related to the participants' limited physical mobility and lack of social contact with others outside of the home environment due to imposed COVID-19 restrictions at the time (eg, stay-at-home mandates, school and church closures, and modified work routines) that in turn improved our accessibility to research participants and increased their willingness to participate in this research.

Discussion

Documentation of psychosocial manifestations among caregivers of children newly diagnosed with FA is becoming more prevalent in the literature. However, interventions to address such manifestations have largely gone unrecognized within the medical community. Further, studies of technology-based interventions that focus on symptom self-management in this population are absent from current literature. Application of mHealth to a variety of chronic health conditions has demonstrated positive associations with self-management

outcomes [22]. The present study will contribute to the body of scientific knowledge by creating, delivering, and evaluating an mHealth, technology-based, scalable, self-management strategy to address the potential physical, emotional, and psychosocial outcomes experienced by caregivers of children newly diagnosed with an FA. By focusing on psychosocial symptoms, such as fatigue, our work will address an unmet need recognized within the literature but neglected by providers. Our scalable strategy to engage caregivers during a critical time period in the caregiving/condition trajectory (≤ 90 days from diagnosis) when psychosocial functioning is at high risk may also reveal other psychosocial manifestations not previously recognized in this specific population. We feel the novel approach of this project has the potential to demonstrate both cost-effectiveness and sustainability. In addition, our work may address barriers to accessing care such as transportation, work schedules, and childcare through the application of technology. Addressing these barriers lends to the translatability of the intervention to other populations of caregivers of children with chronic health conditions.

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Authors' Contributions

BB, KW, and TK conceived of the presented study idea. KW recruited participants for Phase I. BB collected and analyzed Phase I data with support from MP, MM, and TK. BB and MM drafted the manuscript with critical content or editorial contributions from MP, KW, and TK. All authors discussed the final draft of the manuscript and granted approval of the version to be published.

Conflicts of Interest

None declared.

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Abbreviations

- CONSORT:** Consolidated Standards of Reporting Trials
- FA:** food allergy
- FARE:** Food Allergy Education and Research
- FASST:** Food Allergy Symptom Self-Management with Technology for Caregivers
- FIA:** food-induced anaphylaxis
- mHealth:** mobile health
- NIH:** National Institutes of Health
- NINR:** National Institute of Nursing Research
- PI:** principal investigator
- PROMIS:** Patient-Reported Outcomes Measurement Information System
- RA:** research assistant
- RE-AIM:** Reach, Effectiveness, Adoption, Implementation, and Maintenance
- REDCap:** Research Electronic Data Capture

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Protocol

Bovine Lactoferrin to Prevent Neonatal Infections in Low-Birth-Weight Newborns in Pakistan: Protocol for a Three-Arm Double-Blind Randomized Controlled Trial

Shabina Ariff¹, FCPS; Sajid Soofi¹, FCPS; Almas Aamir¹, MA; Michelle D'Almeida², MBBS; Arzina Aziz Ali¹, MBBS; Ashraf Alam², PhD; Michael Dibley³, MPH

¹Department of Pediatric and Child Health, Aga Khan University, Karachi, Pakistan

²School of Public Health, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia

Corresponding Author:

Michael Dibley, MPH

School of Public Health

Faculty of Medicine and Health

The University of Sydney

Rm 328, Edward Ford Building A27

New South Wales

Sydney, 2006

Australia

Phone: 61 407616500

Email: michael.dibley@sydney.edu.au

Abstract

Background: Sepsis is a common and severe complication in premature neonates, particularly those born with low birth weights (<2500 g). Neonatal sepsis is steadily emerging as a leading cause of neonatal mortality in Pakistan. Lactoferrin is a natural product with broad-spectrum antimicrobial properties and glycoprotein that is actively involved in innate immune host responses. Clinical trials have revealed its protective effect on sepsis, but lactoferrin dosage, duration, and role in the prevention of sepsis are still uncertain.

Objective: We aimed to establish the efficacy of bovine lactoferrin in the prevention of late-onset sepsis and to determine the optimal dose and method of administering bovine lactoferrin that may contribute to improvement in overall survival of low birth weight infants.

Methods: We will implement the study in 2 phases at the Aga Khan University Hospital. The first phase, which we have completed, was formative research. This phase mainly focused on a qualitative exploration of perceptions about feeding and caring practices of low birth weight newborns and a trial of improved practices for the preparation and administration of bovine lactoferrin to newborns. The second phase is a 3-arm double-blind randomized controlled trial. In this phase, we randomly allocated 2 different daily oral prophylactic doses of bovine lactoferrin (150 mg or 300 mg) and placebo to 300 low-birth weight neonates starting within the first 72 hours of birth and continuing for the first 28 days of life.

Results: The study protocol was approved by the Ethics Review Committee of Aga Khan University on August 16, 2017. Data collection began in April 2018 and was completed in September 2020. Data analyses are yet to be completed. We expect the results to be published in peer-reviewed journals by autumn of 2021.

Conclusions: This intervention, if effective, has the potential to be translated into a safe, affordable, and widely utilized treatment to prevent sepsis and, subsequently, may improve the survival outcomes of low birth weight neonates in Pakistan and other low- and middle-income countries.

Trial Registration: ClinicalTrials.gov NCT03431558; <https://clinicaltrials.gov/ct2/show/NCT03431558>

International Registered Report Identifier (IRRID): PRR1-10.2196/23994

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KEYWORDS

bovine lactoferrin; low birth weight; sepsis; human milk; premature; mortality

Introduction

Globally, 15.5% of newborns are born with low birth weight, with 96.5% of these births occurring in low-income countries [1]. Approximately 4 million babies in their neonatal period die each year [2]. An estimated 1 million of these deaths occur due to infectious causes, including sepsis, pneumonia, and meningitis, and 60% to 80% of all neonatal deaths are low-birth-weight newborns [1,3]. According to 2018 data, the neonatal mortality rate in Pakistan is 42 per 1000 live births [4]. The current rate of reduction in neonatal mortality is insufficient to achieve United Nations Sustainable Development Goal 3 of reducing neonatal mortality to less than 12 per 1000 live births by 2030 [5].

The incidence of sepsis in neonates is inversely proportional to gestational age and birth weight [6]. Late-onset sepsis is sepsis arising after the perinatal period (>72 hours following birth), which occurs due to microorganisms acquired during the delivery or hospital stay [6,7]. In Pakistan, sepsis caused by multidrug-resistant organisms is common and challenging to treat, resulting in sepsis-related mortality [8]. Late detection, poor sensitivity of diagnostic tests, and nonspecific clinical features further delay the recognition of neonatal sepsis. Furthermore, detection and treatment may not always prevent the high costs of prolonged hospital stays in neonatal intensive care units and late or impaired neurodevelopment. Multiple interventions have been introduced to prevent the morbidity and mortality associated with such serious infections. It is well established that breast milk has beneficial effects against neonatal sepsis in vulnerable populations [9]. This protection is due to the multiple anti-infective, anti-inflammatory, and immunoregulatory factors transmitted through milk. These include secretory antibodies, glycans, lactoferrin, leukocytes, cytokines, and other components produced by the mother's immune system [9].

Lactoferrin is a whey protein in mammalian milk. It has a multifunctional role in host defense via a myriad of antimicrobial and anti-inflammatory functions. The concentration of lactoferrin is highest in colostrum, decreasing as milk matures, and the decrease is slower in the milk of mothers of preterm infants [10]. Bovine lactoferrin shares similar bioactivity and homology (77%) with its isoform, human lactoferrin, and exhibits even higher *in vitro* antimicrobial activity than that exhibited by human lactoferrin [11]. A pilot study [12] in the United States found a protective effect of bovine lactoferrin-enhanced formula (containing 850 mg bovine lactoferrin/L) against lower respiratory tract illnesses in infants compared to that of regular formula. A recent review [13] concluded that lactoferrin was a safe intervention, and its most likely future use in children would be to protect against enteric infections and neonatal sepsis. Furthermore, it concluded that bovine lactoferrin had the potential in to reduce sepsis in low-birth-weight infants and aid in the reduction of child mortality [13]. A randomized clinical trial [14] in India to evaluate the efficacy of bovine lactoferrin in preventing late-onset sepsis in low-birth-weight neonates reported a significant reduction in the incidence of late-onset sepsis in the

bovine lactoferrin supplementation group compared to the placebo.

Despite promising experimental data, clinical information on bovine lactoferrin in infants is scarce, with minimal data from low- and middle-income countries [14]. We sought to address the gaps in the current literature regarding the optimal dose, administration method, and efficacy of bovine lactoferrin in decreasing the incidences of late-onset sepsis and necrotizing enterocolitis in low-birth-weight infants in Pakistan. We also aim to determine the role of bovine lactoferrin supplementation in improving neonatal survival.

The primary objective of this study is to evaluate bovine lactoferrin efficacy in reducing the incidence of late-onset sepsis and to define the optimal daily dose and administration method of bovine lactoferrin to prevent late-onset neonatal sepsis in low-birth-weight and preterm neonates. The secondary objective of this study is to evaluate the effectiveness of bovine lactoferrin in reducing the incidence of necrotizing enterocolitis in low-birth-weight and preterm neonates, and the effectiveness of bovine lactoferrin in improving neonatal survival during the first 28 days of life.

Methods

Study Design

This study consists of 2 phases. The first phase was a qualitative component with formative research and a trial of improved practices. The second phase was a 3-arm double-blind individually randomized controlled trial.

In the first phase, we conducted formative research before the initiation of the clinical trial to explore the acceptability of the delivery of the intervention. We used qualitative research methods, such as in-depth interviews, focus group discussions, and direct observations at the household level, to ascertain the practices and perceptions around feeding and care of low-birth-weight newborns. Based on the information from themes related to adherence, feasibility, and acceptability of bovine lactoferrin use, we carried out an additional trial of improved practices of preparation and administering of bovine lactoferrin to the low-birth-weight newborn by the caregivers at home.

In the second phase, we conducted a 3-arm randomized controlled trial to compare 2 different prophylactic oral doses of bovine lactoferrin (150 mg or 300 mg) and placebo, given daily over the first 28 days of life. We initiated the treatment within the first 72 hours following birth.

Study Setting

This study was conducted at the Aga Khan University Hospital in Karachi, Pakistan, in collaboration with researchers from the School of Public Health, the University of Sydney, Australia. The Aga Khan University Hospital is a state-of-the-art Joint Commission International accredited tertiary care hospital and has 2 postnatal wards with a fully equipped 24-bed neonatal intensive care unit with an extensive clinical support unit. Annually, approximately 5500 deliveries take place with a known prevalence of 15% to 18% for low-birth-weight neonates.

The hospital also has a clinical trial unit, laboratory, and pharmacy, along with other essential hospital services to conduct clinical trials.

Study Population and Eligibility Criteria

For the formative research, we recruited women, their husbands, and mothers or mothers-in-law from Aga Khan University Hospital, and the qualitative researcher made an appointment to interview them at the hospital using a standard structured questionnaire. The trial participants, parents with low-birth-weight neonates (birth weight <2500 g and \geq 1000 g) in each treatment group, were recruited from the Aga Khan University Hospital. All low-birth-weight neonates with gestational age from 28 weeks to 36 weeks 5 days, with no sign of sepsis, and on oral feeding within 72 hours of birth were eligible. We obtained written informed consent from parents or caregivers after assurance that the family planned to stay in the study area for at least 1 month.

Exclusion criteria were neonates with congenital anomalies, culture-proven early-onset sepsis, history of severe maternal chorioamnionitis, or group B streptococcus colonization during pregnancy, gestational age less than 27 weeks 6 days, birth weight less than 1000 g, and parental refusal to consent.

Sample Size

Phase 1: Formative Research

Following the inclusion criteria, 10-15 low-birth-weight neonates' parents or caregivers were recruited purposively for the trial of improved practices. We conducted 30 in-depth interviews.

Phase 2: Clinical Trial

A total of 100 low-birth-weight neonates were enrolled in each group, leading to an aggregate of 300 neonates. We estimate that the sample size with a 2-sided α of 5%, power of 80%, and 10% lost to follow up. Based on current hospital data, the incidence of neonatal sepsis in the placebo group is 25%. We conducted 30 in-depth interviews with parents and caregivers of low-birth-weight infants. We enrolled 15 low-birth-weight infants for trial of improved practices. Based on these assumptions, the required sample size in each trial arm was calculated as 95 low-birth-weight neonates (rounded to 100 low-birth-weight neonates), leading to a total of 300 low-birth-weight neonates.

Randomization, Allocation, and Masking

An independent statistician from the University of Sydney produced a computer-generated random allocation sequence using Stata (version 15; StataCorp LLC) software with a 1:1:1 ratio for the 3 arms of the trial (an allocation probability of one-third per treatment arm) and a block size of 9 for approximately anticipated number of newborns recruited each day.

Once an infant met the eligibility criteria, we provided an information sheet to the parents, in English and the local language, explaining (1) the benefits of lactoferrin as a nutritional supplement along with the method of administration and (2) the placebo and its ingredients. Informed consent was

obtained from the parents, after which we enrolled the neonates in the study. We blinded the participants and study teams to the group allocation. We delivered the treatment kits to the study site before initiation of the study.

Intervention

We will evaluate 2 different strengths (150 mg and 300 mg) of bovine lactoferrin as the intervention treatment. The color of bovine lactoferrin powder in each intervention and placebo (D-Glucose) are identical in appearance. The study staff administered the first oral dose of the trial supplement to the neonate at the hospital in the presence of the mother or the caregiver on the third day of life with a single daily dose mixed with milk (preferentially breast milk otherwise formula milk) and the mother or caregiver continued to administer the supplement/placebo for 28 days. We stored the supplement sachets at room temperature and maintained an inventory at the clinical trial unit at the Aga Khan University Hospital. We monitored adherence by weekly collection of used empty sachets from the parents before providing them with the next set of sachets for the subsequent week.

Retention and Follow-up

We followed the newborns weekly (for 28 ± 2 days) for general well-being, recognition of danger signs, and adherence to supplementation. Daily follow-ups were completed during the hospital stay until discharge. At the time of discharge, we provided the participants with 1 week's supply of supplements. A telephone follow-up was conducted midweek, and a home visit was conducted once a week. The study investigators conducted the first follow-up visit after discharge from the neonatal care unit.

Data Collection and Management

The research team captured data electronically using tablets equipped with special-purpose programs. We ran a pilot before the implementation of the trial to avoid technical errors. The tablets transferred the captured data to a secured database on the server at Aga Khan University with a secure copy at the University of Sydney.

At each follow-up visit, at home or at the hospital, a questionnaire was administered about the history of illnesses and feeding practices during the previous week. The criteria for identifying a baby with presumed clinical sepsis included any signs or symptoms such as lethargy, apnea, tachypnea, respiratory distress, reluctance to feed, temperature instability, feed intolerance, vomiting, aspirates, abdominal distention, and seizures. We define sepsis as a baby with any of the criteria of presumed sepsis in addition to either increased C-reactive protein level (>1 mg/dL) or an increased or decreased white blood cell count (7.0 - 23.0×10^3 /uL), hypoglycemia (<40 mg/dL), or positive blood culture.

We conducted a complete physical examination on every visit. In addition, anthropometric measurements were taken at birth, on day 14, and on day 28. If any of the above symptoms were found or there was clinical suspicion of sepsis in a neonate, we performed a workup (sepsis screen) according to the standard

protocol of the hospital, which includes complete blood count, C-reactive protein level, blood culture, and admission.

Statistical Analysis

We will use SPSS software (version 19.0; IBM Corp) for statistical analysis. For continuous data, we will report the mean and standard deviation or median and interquartile range. We will report the baseline characteristics of the study population with frequencies and percentages. To compare categorical variables, we will use chi-square tests, and to compare continuous variables, we will use paired *t* tests. To assess the outcome variable, incident neonatal sepsis, we will use applied logistic regression and report odds ratios and 95% confidence intervals for all predictor variables. Initially, we will conduct bivariate logistic regression analyses to estimate an unadjusted odds ratio for each variable. We will examine the predictors that demonstrate an association with the outcome (P value $<.25$) in multiple logistic regression models. We will consider a P value $\leq .05$ as significant.

Safety Reporting

Previously published evidence shows that orally administered lactoferrin decreases sepsis and necrotizing enterocolitis in preterm neonates without any adverse effects [15,16]; however, if any adverse events occur, it will be reported in accordance with local institutional ethics committee policies. We will define an adverse event as any untoward medical occurrence in a trial participant who has been administered the trial product and which does not necessarily have a causal relationship with the treatment.

Serious adverse events will be any untoward medical occurrence that at any dose results in death, is life-threatening (ie, the infant is at risk of death at the time of the event), requires inpatient hospitalization or prolongation of existing hospitalization, or other important medical events which, in the opinion of the investigator, are likely to become serious if untreated.

A suspected unexpected serious adverse reaction will be defined as an serious adverse event that is related to the drug or device and is unexpected (ie, not listed in the investigator brochure or approved Product Information and Informed Consent Form [17]).

Ethical Approval and Consent to Participate

The Ethics Review Committee of the Aga Khan University approved the study (ID 4873-Ped-ERC-17). The National Bioethics Committee of Pakistan granted approval for the study to be conducted on human participants. The study was also approved by the Research Integrity & Ethics Administration, Human Research Ethics Committee, The University of Sydney (ID 2017/420).

Written informed consent was obtained from all study participants prior to enrollment in the study. We will take special care to ensure the confidentiality and privacy of the study participants' medical histories and personal information. We will store all sources of information in a password-protected predefined program, using tablets (at the time of enrollment and subsequent follow-up visits) at the Data Management Unit (The Aga Khan University). All source documents will be maintained

in locked files and will only be available to people directly involved in the study.

Results

The study protocol was approved on August 16, 2017. Data collection began in April 2018 and was completed in September 2020. Data analyses are yet to be completed. We expect the results to be published in peer-reviewed journals by autumn 2021.

Discussion

This study will provide information on the effectiveness of bovine lactoferrin in preventing late-onset neonatal sepsis in low-birth-weight neonates and will be used to identify the optimal dosage and administration method. Our study approach aims to prevent neonatal infections; current treatment approaches involve treating neonatal infections when they occur. The current approach, which focuses on early detection of infections in newborns through postnatal care and treatment with antibiotics, runs the risk of worsening antimicrobial resistance, which is already an emerging crisis. Our approach, through the use of prophylactic bovine lactoferrin supplements, will be cost-effective, greatly reduce the risk of microbial resistance to antibiotics, and can be implemented in all settings through various health care providers who would initiate the treatment.

A review [15] of clinical trials found that despite the small sample size, the preliminary results of the trials showed a positive effect of lactoferrin on the prevention of neonatal infections. It also concluded that if proven to be effective, lactoferrin can become a cost-effective intervention that can potentially impact neonatal mortality and morbidity worldwide [15]. In a 2017 Cochrane review [16], enteral lactoferrin was found to reduce the rate of late-onset sepsis (risk ratio 0.59, 95% CI 0.40-0.87; $P=.008$; from 6 trials with 886 participants) and the rate of necrotizing enterocolitis (risk ratio 0.40, 0.18-0.86; $P=.02$; from 4 trials with 750 participants) in preterm neonates. The review [16] also concluded that although lactoferrin holds great potential for late-onset sepsis and necrotizing enterocolitis prevention, multiple questions still need to be answered, including the administration method and optimal dosage. Our study aims to address these gaps in the current literature.

This intervention, if effective, has the potential to be translated into a safe, affordable, and widely utilized intervention to prevent sepsis and subsequently improve survival in low-birth-weight neonates in Pakistan and other low-and middle-income countries. Following the achievement of conclusive results, we plan to scale up the intervention. Our long-term vision is to produce lactoferrin within Pakistan as a byproduct of the dairy industry, for use as part of the standard neonatal care package for the support of low-birth-weight babies, delivered both in hospital and at home.

The results of this trial will be disseminated to the government, academic, and policy-making communities, as well as to the wider public in a peer-reviewed journal and at relevant national and international conferences.

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Authors' Contributions

SA is principal investigator of the trial. SA, SBS, and MD designed the study. SA, AA, MD, A, and AAA contributed to writing initial drafts of the manuscript and critically reviewed the manuscript. All authors read and approved the final version.

Conflicts of Interest

None declared.

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Protocol

Home-Based Intervention for the Prevention and Treatment of Malaria Among Children Younger Than 5 Years in the West Region of Cameroon: Protocol for a Randomized Controlled Trial

Esther Dongmo Kenfack¹, MPH; Nicholas Tendongfor¹, PhD; Dickson Shey Nsagha¹, PhD

Department of Public Health and Hygiene, Faculty of Health Sciences, University of Buea, Buea, Cameroon

Corresponding Author:

Dickson Shey Nsagha, PhD

Department of Public Health and Hygiene

Faculty of Health Sciences

University of Buea

P.O. Box 63, Molyko

Buea

Cameroon

Phone: 237 677499429 ext 699674201

Email: nsaghads@hotmail.com

Abstract

Background: Although malaria is preventable and curable, 1 child dies of this disease every 2 minutes in Africa. Home-based management of malaria reduces the progression of severe malaria by more than 50%. Scalable, efficacious, and cost-effective strategies are needed to empower the capacities of home caregivers of children younger than 5 years of age in health education, diagnosis, and treatment of malaria at home.

Objective: The main objective of this trial is to assess the impact of the management provided by home caregivers on the prevention, diagnosis, and treatment of malaria in children younger than 5 years as compared to the home-based malaria management component of the integrated community-directed intervention (CDI) strategy of community health workers (CHWs).

Methods: A randomized controlled trial will be conducted. CHWs have conducted a census of all households where there is at least one child younger than 5 years with their home caregivers. These children and their home caregivers have been randomly placed into the intervention or control groups among the households identified. The trial will allow malaria home-based prevention, diagnosis, and treatment of 350 children younger than 5 years old by home caregivers in the Fombap area (intervention group) where the integrated CDI strategy will not be implemented. This group will be compared to the home-based malaria management component of the integrated CDI strategy in which 350 children in the same age group will be followed up by CHWs in the Baneghang area (control group). The primary outcomes will be the prevention, diagnosis, and treatment of malaria in children younger than 5 years of age by home caregivers at home. The secondary outcomes comprise the malaria follow-up indicators produced by home caregivers in the intervention group and those produced by CHWs in the control group. Both descriptive and one-way analysis of variance estimation techniques will be used to compare the mean difference in the 2 strategies.

Results: From September 2019 to October 2019, all home caregivers with children younger than 5 years of age were identified in the intervention and control group by CHWs. Following this, 203 home caregivers with their 350 children younger than 5 years were randomly selected and enrolled in the intervention group, while 225 home caregivers with their 350 children younger than 5 years were enrolled in the control group. In the intervention group, 203 home caregivers were trained in November 2019. This home treatment effectively started in December 2019 and will continue until May 2020.

Conclusions: Findings from this randomized controlled trial will contribute to resolving the challenges of severe malaria and to limiting the death due to malaria of children younger than 5 years. This will bring benefits to home caregivers who will know how to promptly diagnose and properly treat malaria in their children at home.

Trial Registration: Pan African Clinical Trial Registry (PACTR) 202003487018009; <https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=9788>

International Registered Report Identifier (IRRID): DERR1-10.2196/19633

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KEYWORDS

home-based management; malaria; children younger than 5 years; home caregivers; West Region; Cameroon

Introduction

About 700,000 to 2.7 million people die of malaria each year, 75% of whom are African children [1]. There were also 435,000 malaria deaths worldwide in 2017, mostly in Africa, the majority being children younger than 5 years of age, with 1 child dying every 2 minutes from this preventable and curable disease [2]. In Africa, more than 70% of malaria cases in rural areas and more than 50% of cases in urban areas are self-treated, and formal health care is sought only if initial treatment fails [3]. According to World Malaria Report 2018, similar to the top 10 most affected African countries, Cameroon recorded an increase of about 131,000 additional cases of malaria compared to the previous year [2]. The report also revealed an insufficient level of access to resources and interventions for an effective fight against malaria [2].

Most parents go to street vendors rather than to the health care system for their medications. Many studies have shown that the majority of early treatments for childhood fever are given at home [4,5] and that these treatments are usually incorrect or suboptimal [6,7].

More than 90% of sick children in rural areas in Senegal receive their first treatment at home; unfortunately, most of the time, they receive inappropriate self-medication [8]. The majority of malaria cases are recorded in households rather than in health care facilities, as they are inaccessible to the majority of those with malaria. National surveys in the World Health Organization (WHO) African Region indicate that only about one-third of febrile children receive consultation from qualified health staff [9]. Early access to effective malaria treatment is one of the main strategies for reducing the burden of malaria. This means that treatment must be available and as close to the homes as possible within 24 hours from the onset of symptoms.

Home-based management of malaria (HMM) including diagnosis by rapid diagnosis test (RDT) and treatment based on test results is a promising strategy to improve the access of remote populations to prompt and effective management of uncomplicated malaria and to decrease mortality due to malaria [10]. It has been acknowledged that it is time to intensify the HMM in endemic countries to cover the majority of their populations, and that this will result in early access to good quality antimalarial drugs at appropriate doses within 24 hours from the onset of symptoms [10]. Accumulated experience shows that it is possible to improve malaria management in the household at the community level and to reduce morbidity and mortality [11].

Studies show that HMM reduces the progression of severe malaria by more than 50% and reduces the overall mortality of children younger than 5 years old by 40% [12,13]. It is now generally accepted that with appropriate training and use of prepackaged drugs, mothers can recognize fever and administer timely and appropriate treatment [12]. In the framework of successful programs, mothers, as primary home health caregivers for their children, have been trained in the early recognition of

malaria symptoms and administration of appropriate treatment [12]. The ability of mothers or home caregivers to recognize malaria and administer prompt and appropriate treatment resulted in a 40% reduction in overall mortality in children younger than 5 years old in the program area [13].

In 2001, the WHO recommended an equity strategy aimed at improving access to essential care for children younger than 5 years old through the introduction of HMM [14]. In 2010, they recommended confirmation of diagnosis by microscopy or RDT before any treatment [15]. This ensures early recognition and prompt and appropriate response (treatment) to malarial illness in children younger than 5 years within the home or the community [14]. This strategy aims to enable home caregivers to recognize malaria early and respond appropriately, to ensure that home caregivers have adequate knowledge and capacity to respond to malaria, and to create an environment that enables the strategy to be implemented by making medicines available as near to the home as possible [14]. In Senegal, a pilot study on HMM conducted in 2008 demonstrated the feasibility of integrated use of RDTs and artemisinin-based combination therapy in isolated villages by volunteer home health caregivers [10]. HMM that includes RDT and treatment based on test results is a promising strategy for improving the access of isolated populations to an early and effective management of uncomplicated malaria and for reducing malaria mortality [10]. Home caregivers have demonstrated excellent adherence to guidelines, potentially contributing to a decrease in malaria-related deaths in the community [10].

Recently, successful introduction of RDTs into HMM programs has been reported in several African countries, including Cameroon [16,17]. However, the integrated community-directed intervention (CDI) strategy has only been implemented in some health districts in Cameroon. Thus, the interventions have not been made available, particularly for children younger than 5 years; yet, this age group constitutes a vulnerable population. Innovative interventions are needed at all levels, particularly concerning prompt and effective malaria management cases, a key strategy recommended by the WHO [18].

It is very strategic to use home caregivers (mothers of children for instance) for diagnosis and administration of antimalarial treatment because they are the ones who provide first aid to their children. Community health workers (CHWs) can supplement home caregivers in their work by providing more health education, resupplying household care kits, and seeking better access to medicines. Therefore, a strategy to train home caregivers on the diagnosis and administration of malaria treatment is particularly appropriate for achieving more complete coverage. The goals of the strategy are to ensure the early recognition and prompt and effective response to malaria at home, especially for children younger than 5 years old. This strategy will not only reduce the workload of CHWs, but will also solve the unavailability and distance problem that involves people having to walk to meet the CHW for treatment. The aim of the study is to investigate the impact of a home-based

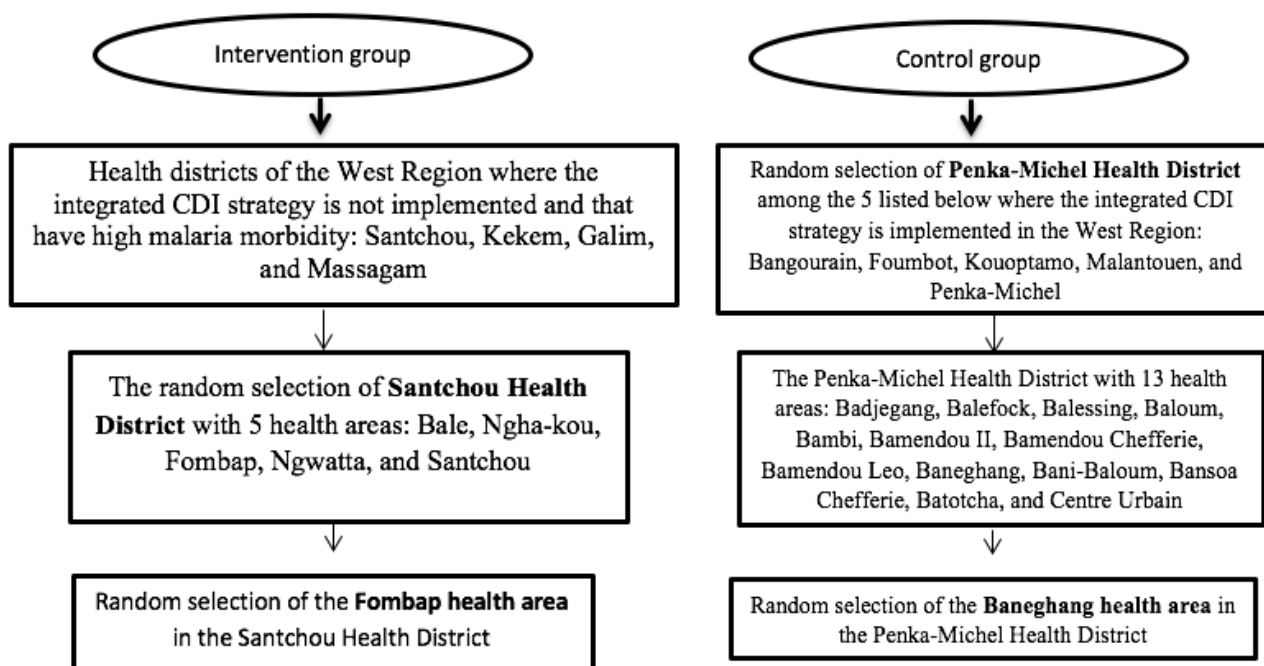
intervention strategy for the prevention, diagnosis, and treatment of malaria in children younger than 5 years. We hypothesize that an intervention aimed at empowering home caregivers can make the prevention, diagnosis, and treatment of malaria in children younger than 5 years at home better than those under the integrated CDI strategy of CHWs.

Methods

Study Area

This study will be community-based, occurring in 2 health areas of the West Region of Cameroon: the Fombap health area in

Figure 1. Flow chart of the sampling frame for the selection of 2 groups. CDI: community-directed intervention.



Study Design

The study will use a randomized controlled trial design. The trial was registered with the Pan African Clinical Trial Registry (202003487018009) in South Africa on March 18, 2020. It will be a community-based study examining the impact and effectiveness of the home-based malaria prevention, diagnosis, and treatment of children younger than 5 years by home caregivers (intervention) as compared to the home-based malaria management component of the integrated CDI strategy of CHWs (control). Children younger than 5 years and their home caregivers have been randomly placed into the intervention and control groups after the completion of a census of all households in the area by CHWs. In the intervention group, home caregivers will be trained to perform the RDT and administer the treatment (artesunate-amodiaquine) to children younger than 5 years for prompt and effective management at home. CHWs will be responsible for providing health education and for supplying households with malaria kits. In the control group, children younger than 5 years will be followed up through the malaria indicators produced by CHWs.

Santchou Health District where the integrated CDI strategy will not be implemented (intervention group) and the Baneghang health area in Penka-Michel Health District where the integrated CDI strategy is being implemented (control group).

Figure 1 shows the multistage sampling approach, in which probability and nonprobability sampling methods were used to select the 2 health areas.

Sample Size Calculation

The sample size calculation for this trial study will be based on the following formula for comparing 2 groups [19]:

$$n = \frac{Z_{\alpha/2}^2 \cdot p \cdot (1-p)}{d^2}$$

where $p_1 = 0.44$, $p_2 = 0.33$, $Z_{\alpha/2} = Z_{0.05/2} = 1.96$ (from z table or type 1 error of 5%), $Z_{\beta/2} = z_{0.20} = 0.842$ (from z table at 80%), and $p = \text{pooled prevalence} = (\text{prevalence in intervention group } (p_1) + \text{prevalence in control group } (p_2))/2$.

$$n = \frac{Z_{\alpha/2}^2 \cdot p \cdot (1-p)}{d^2} + \frac{Z_{\beta/2}^2 \cdot p \cdot (1-p)}{d^2}$$

$$n = 300$$

With a 15% nonresponse rate, the sample size is rounded up to 350 children younger than 5 years being assigned to the intervention group and 350 being assigned to the control group.

Inclusion and Exclusion Criteria

The inclusion criteria will be households with at least one child younger than 5 years and their home caregivers who are between 18 years and 60 years of age and who take care of these children.

The exclusion criteria will be children younger than 2 months and home caregivers who do not give their consent.

Data Collection Procedure

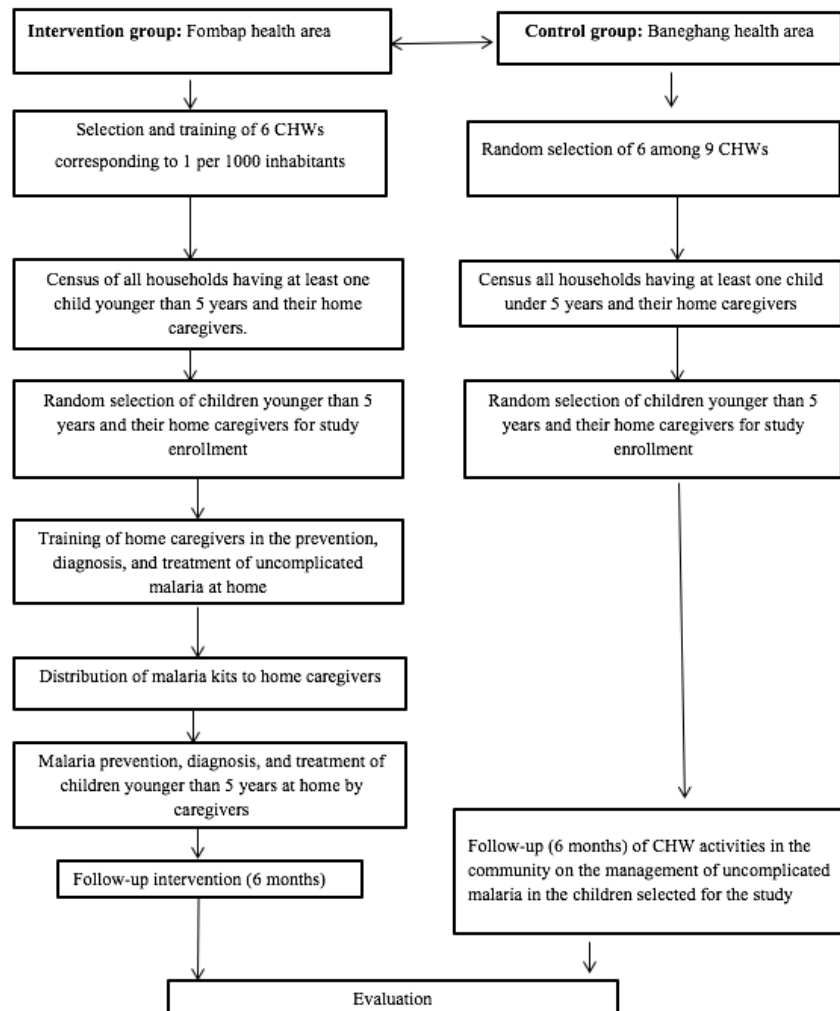
Trained interviewers were blinded to group allocation and collected data using pretested questionnaires. For baseline data, a pretested questionnaire was administered to home caregivers on the perception (knowledge, attitudes, and practices) of malaria. This questionnaire will be repeated at the end of the intervention. During the intervention, a structured data collection form will be used and will contain monthly malaria follow-up indicators recorded by home caregivers in the intervention group and the malaria follow-up indicators recorded by CHWs in the control group. The data source for the study will be the malaria register used for the intervention in the Fombap health area and the malaria register used by the CHWs in the Baneghang health area.

In the experimental group (Fombap health area), 6 CHWs were chosen from the Fombap population of 5875 inhabitants,

corresponding to 1 CHW per 1000 inhabitants. In each CHW's zone, the CHW conducted a census of all the households where there is at least one child younger than 5 years and their home caregiver. From this census, children younger than 5 years old and their home caregivers were randomly selected for enrollment in the study. They will be trained in the prevention, diagnosis, and treatment of uncomplicated malaria at home. Malaria kits will be distributed to home caregivers to take care of the children younger than 5 years at home.

With Baneghang health area as the control group, 6 CHWs were also randomly selected from the 9 in the Baneghang health area. In each CHW's zone, the CHW conducted a census in all the households where there is at least at least one child younger than 5 years and their home caregiver. After the households were identified, children younger than 5 years old and their home caregivers were randomly selected for enrollment in the study. [Figure 2](#) shows the outline of the sampling method for the intervention.

Figure 2. Flow chart showing the sampling method for the intervention study.



Ethical Considerations

Ethical approval has been obtained from the Faculty of Health Sciences Institutional Review Board of the Buea University (reference no. 2019/1023-09/UB/SG/IRB/FHS). Administrative authorization has been obtained from the University of Buea,

the Regional Delegation of Public Health for the West Region, and the health districts of Santchou and Penka-Michel.

Participation of individuals and households will be strictly voluntary and on the basis of informed written consent and assent by the household heads or caregivers. The purpose of the

study and the role of the participants will be well explained in the consent form. Once informed consent and assent are obtained from the participants, research staff will collect baseline data, and will conduct the intervention and postintervention.

Intervention Development

In order to contribute to the improvement of the HMM component of the integrated CDI strategy, an intervention will be implemented to make home caregivers accountable for the malaria prevention, diagnosis, and treatment at home. This strategy will be used in the Fombap health area where the integrated CDI strategy will not be implemented. The intervention was designed with the active participation of CHWs and home caregivers in the management of malaria at home through their training. Participants in this study will be made aware that the training they receive will give them the opportunity to test and treat malaria in their children younger than 5 years of age at home. Thus, this intervention will enhance home caregivers’ capacities to prevent, diagnose, and treat malaria at home in their children younger than 5 years. The different steps will be the selection of CHWs, the census of households with at least one child younger than 5 years and their home caregivers, the training of CHWs and home caregivers, the provision and the management of malaria kits, the health education of home caregivers on malaria prevention measures, and the monitoring and evaluation of the activities.

Step 1: The Selection of Community Health Workers

In the intervention group, the identification and selection of CHWs will be carried out in collaboration with the head of the

health area and the leaders of all communities. A meeting will be convened at the Fombap Higher Chiefdom during which CHWs in each community will be selected. Then, 6 CHWs will be selected in the intervention group and 6 CHWs will be randomly selected among the 9 existing in the control group.

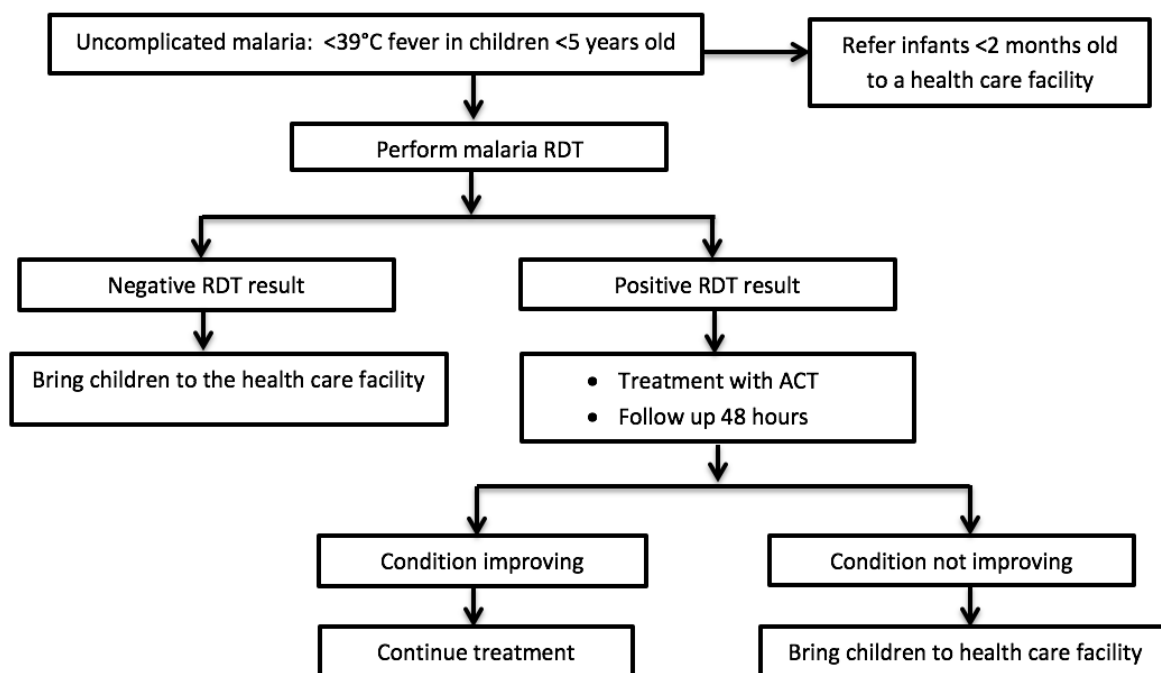
Step 2: The Census of Households, Children Younger Than 5 Years, and Home Caregivers

The CHWs in their respective zones identified and recorded all households with at least one child younger than 5 years and their home caregivers. After identifying the households, the children younger than 5 years and their home caregivers were randomly selected by the researchers for enrollment in the study.

Step 3: The Training of CHWs and Home Caregivers

The selected CHWs will be trained by the research team, and home caregivers will be trained by the research team with the help of the CHWs. The training will be focused on malaria management of children younger than 5 years at home and will include recognizing uncomplicated malaria (base on sign and symptoms), performing malaria RDT, administering artesunate-amodiaquine to children in the case of a positive test, and referring RDT-negative children or those with severe malaria to the health care center. The training process will be based on the training handbook of the Cameroon Ministry of Public Health. The training module of the CHW modified version will be used, as it is simple and has practical demonstrations to enhance understanding. The algorithm used in our study (Figure 3) will be adapted from that used in Senegal [10].

Figure 3. Algorithm for the home management of malaria adapted from that used in Senegal. ACT: artemisinin-based combination therapy; RDT: rapid diagnosis test.



Step 4: The Provision and Management of Malaria Kits

SD Bioline Malaria Ag Pf RDT is used in Cameroon and meets the performance criteria recommended by the WHO [20], while

a fixed dose of artesunate-amodiaquine is a combination used as first-line treatment in Cameroon [21]. RDTs and malaria kits will be distributed during the training to all home caregivers, and then the CHWs will take care of replacing kits in

households. The malaria kits will be provided to CHWs by the research supervisor according to the need expressed. The support kit will consist of a thermometer, 2 RDTs, a packet of 25 mg/67.5 mg of artesunate-amodiaquine and/or 50 mg/135 mg of artesunate-amodiaquine, a packet of paracetamol, and an algorithm chart for malaria management. In case of any fever above 38°C in the children younger than 5 years of age as confirmed by the thermometer and without any other sign of gravity, the home caregiver will conduct an RDT of malaria. If the test result is positive, the caregiver will administer the child artesunate-amodiaquine and paracetamol; if the result of the test is negative, the caregiver will take the child to a health center for in-depth exams and treatment for the other causes of fever. For statistical purposes and to replace their kits, home caregivers will inform the CHW of their community by phone of the results of the test and the treatment received by their child. Malaria kits will be distributed free of charge for children younger than 5 years old and this will be purchased from the national provision fund. This study is funded by EDK.

Step 5: The Health Education of Home Caregivers

CHWs will provide health education to the home caregivers concerning malaria prevention measures, the advantages of HMM, and the role of home caregivers in the health care of children. Health education will focus on malaria prevention measures, such as cleaning around the house, the use of insecticide-treated mosquito nets, the use of window screens, the use of insecticides, and the closure of doors and windows before nightfall. CHWs will also explain the concept of home-based prevention and treatment of malaria and the possibility of treating uncomplicated malaria in the community and even in the home. They will also explain that if the diagnosis and treatment of uncomplicated malaria occurs within 24 hours, the condition usually progresses to cure, whereas if early diagnosis and treatment do not occur, the condition can progress to severe malaria and even death. CHWs will provide health education to home caregivers by going door-to-door once a week to at least 5 households and will also go once a month to meetings of women in their area. They will also go to replace the malaria kits in any household that has a suspected case.

Step 6: Monitoring and Evaluation Activities

The monitoring of the activities will be carried out by the research supervisor, the head of the health area, and the researchers to compile and evaluate the work completed on the

field. A meeting will be organized twice a month, bringing together the research supervisor and the CHWs to monitor activities. For statistical purposes and to replace their kits, home caregivers will inform CHWs in their community of all suspected malaria cases in the children younger than 5 years, of the result of RDTs, and of the malaria treatment received by the child. Each month, the monitoring indicators produced by the home caregivers will be collected by CHWs for evaluation purposes. An evaluation of the activities will be carried out monthly during the period of intervention.

After the intervention, a descriptive, analytical, and comparative study will be made in the Baneghang and Fombap health areas to compare the two strategies. This evaluation will be based on the HMM follow-up indicators reported by home caregivers in the intervention group and will be compared to those of the CHWs in the control group.

The Control Group

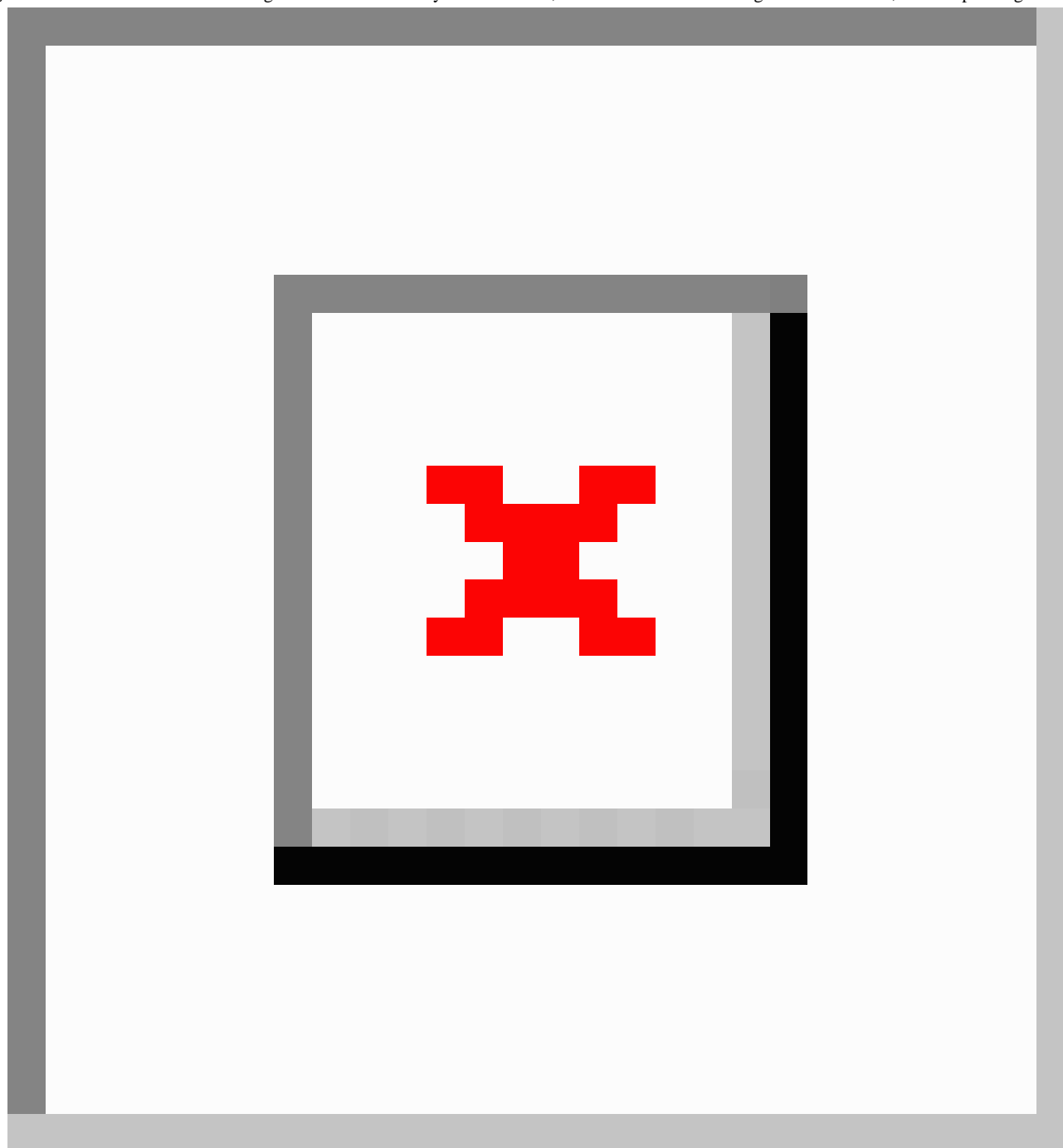
The integrated CDI strategy is implemented in 5 health districts in the West Cameroon region, including the Penka-Michel Health District, from which our control health area, Baneghang, was randomly selected for the site of the control group. In this area, the malaria management component of the integrated CDI strategy is carried out by 9 CHWs, 6 of whom were randomly selected for the study. CHWs conducted a census in their respective zone of all the households where there is at least one child younger than 5 years and their home caregivers. After identifying the households, children younger than 5 years old and their home caregivers were randomly selected for enrollment in the study.

Usually, when there is a suspected case of malaria in the community, the patient is taken to the CHW's home. The patient is examined by the CHW to check for uncomplicated malaria. If the test is positive, the CHW conducts an RDT and administers malaria treatment; if the test is negative, the CHW refers these patients and those with severe malaria to the health care center and makes home visits to provide health education to parents.

Presentation of the Two Strategies

Figure 4 shows the current strategy put in place by the Ministry of Public Health through the integrated CDI and intervention approaches.

Figure 4. Flow chart of the two strategies. CHW: community health worker; HMM: home-based management of malaria; RDT: rapid diagnosis test.



Outcome Measures

Primary Outcomes

The primary outcomes will be the prevention, diagnosis, and treatment of malaria in children younger than 5 years of age by home caregivers at home as measured by comparing malaria follow-up indicators produced by home caregivers in the intervention area to those produced by CHWs in the control group.

Secondary Outcomes

The secondary outcomes will be the proportions of malaria follow-up indicators, including the proportion of suspected malaria cases, the proportion of confirmed malaria cases, the

proportion of confirmed malaria cases who have received artesunate-amodiaquine, the proportion of children younger than 5 years referred to and who received treatment in health care facilities in the health area, and the proportion of household visits made by CHWs.

Data Management and Analysis

Data management and statistical analysis conducted during the intervention will be entered into the research log book and checked by a statistician. All data will be encoded and accessible only to those allowed by EDK The local ethics committee has already approved the study and confirmed the detailed specifications on data security provided to them. The data will be later keyed into a computer using Microsoft Excel 2016

(Microsoft Corporation) and checked for input errors. Descriptive analyses will be conducted using mean, SD, median, IQR, and counts, based on distribution. To investigate the effects of the intervention, a comparison of the pre- and postintervention data will be conducted using the Wilcoxon signed-rank test for the indicators of the malaria. For group comparisons, the *t* test will be used to compare means, while the chi-square test will be used to compare the proportions of malaria home-based management indicators in the intervention and control groups. Differences will be considered statistically significant at a *P* value <.05. Missing data will be handled using the multiple imputation method.

Results

In August 2019, 6 CHWs were selected with the help of the community. From September 2019 to October 2019, 408 home caregivers with their 715 children younger than 5 years were identified in the intervention area by CHWs. Among them, 350 children younger than 5 years old and their 203 home caregivers were randomly selected and enrolled in the intervention group. In addition, CHWs identified 451 home caregivers with their 708 children younger than 5 years old. Among them, 350 children younger than 5 years old and their 225 home caregivers were randomly enrolled in the control group.

In the intervention group, 203 home caregivers were trained in November 2019 to prevent and treat malaria at home for their children younger than 5 years. Diagnostic kits (RDTs and thermometers) and treatment (artemunate-amodiaquine and paracetamol) were distributed to these home caregivers during the training. Home treatment effectively started in December 2019 and will continue until May 2020. The baseline data have already been collected and are being analyzed.

Discussion

The goal of this study is to examine the impact of a home-based intervention strategy for the prevention and treatment of malaria in children younger than 5 years of age. Home-based

management of malaria including diagnosis by RDT and treatment based on test results is a promising strategy to improve the access of remote populations to prompt and effective management of uncomplicated malaria and to decrease mortality due to malaria [10]. The home-based prevention, diagnosis, and treatment of malaria of children younger than 5 years of age is aimed at providing this group with prompt diagnosis and appropriate treatment in order to reduce severe malaria, which is the leading cause of death in children younger than 5 years.

The prevention phase of malaria consists of providing door-to-door health education to the home caregivers, which includes malaria prevention measures, such as cleaning around the house, the use of insecticide-treated mosquito nets, the use of window screens, the use of insecticides, and the closure of doors and windows before nightfall.

The management of malaria phase consists of training and providing home caregivers with malaria kits to conduct prompt diagnose and appropriate treatment of children younger than 5 years at home. Home caregivers have demonstrated excellent adherence to guidelines, potentially contributing to a decrease in malaria-related deaths in the community [10]. Our study design provides opportunities for evaluating the effectiveness of home caregiver-based prevention, diagnosis, and treatment at home for malaria in children younger than 5 years as compared to that of community treatment by CHWs. In the evaluation of each intervention's cost-effectiveness for the primary outcomes, we hypothesize that each intervention will improve the efficacy of the home-based management of malaria.

Findings from this randomized controlled trial may contribute to resolving the challenges of severe malaria and to reducing the deaths of children younger than 5 years due to malaria. Our results may further create greater benefits for home caregivers who will be able to promptly diagnose and appropriately treat malaria in their children at home. The findings will inform public health authorities on the impact of a home-based strategy for the prevention, diagnosis, and treatment of malaria in children in Cameroon.

Acknowledgments

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Authors' Contributions

EKD conceived and designed the study, analyzed the data, wrote the first draft of the manuscript, and revised it. NT supervised the work and methods, and proofread the manuscript. DSN conceived the study, supervised the work, and revised the manuscript. All authors read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

CONSORT eHealth checklist (V 1.6.1).

[[PDF File \(Adobe PDF File\), 10811 KB - resprot_v10i3e19633_app1.pdf](#)]

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Abbreviations

- CDI:** community-directed intervention
CHW: community health worker
HMM: home-based management of malaria
RDT: rapid diagnosis test
WHO: World Health Organization

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Protocol

The Neurostimulation of the Brain in Depression Trial: Protocol for a Randomized Controlled Trial of Transcranial Direct Current Stimulation in Treatment-Resistant Depression

Raheem Suleman¹, BSc, MD; Benjamin V Tucker², MA, PhD; Serdar M Dursun^{1,3}, MD, PhD; Michael L Demas^{1,3}, MD

¹Department of Psychiatry, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB, Canada

²Department of Linguistics, Faculty of Arts, University of Alberta, Edmonton, AB, Canada

³Grey Nuns Community Hospital, Edmonton, AB, Canada

Corresponding Author:

Raheem Suleman, BSc, MD

Department of Psychiatry

Faculty of Medicine and Dentistry

University of Alberta

1E1 Walter Mackenzie Health Sciences Centre, University of Alberta

8440-112 St NW

Edmonton, AB, T6G 2B7

Canada

Phone: 1 7804076504

Email: rsuleman@ualberta.ca

Abstract

Background: Major depressive disorder (MDD) is the second highest cause of disability worldwide. Standard treatments for MDD include medicine and talk therapy; however, approximately 1 in 5 Canadians fail to respond to these approaches and must consider alternatives. Transcranial direct current stimulation (tDCS) is a safe, noninvasive method that uses electrical stimulation to change the activation pattern of different brain regions. By targeting those regions known to be affected in MDD, tDCS may be useful in ameliorating treatment-resistant depression.

Objective: The objective of the Neurostimulation of the Brain in Depression trial is to compare the effectiveness of active versus sham tDCS in treating patients with ultraresistant MDD. The primary outcome will be the improvement in depressive symptoms, as measured by the change on the Montgomery-Asberg Depression Rating Scale. Secondary outcomes will include changes in the Quick Inventory of Depressive Symptomatology Scale (subjective assessment), the World Health Organization Disability Assessment Schedule 2.0 (functional assessment), and the Screen for Cognitive Impairment in Psychiatry (cognitive assessment). Adverse events will be captured using the Young Mania Rating Scale; tDCS Adverse Events Questionnaire; Frequency, Intensity, and Burden of Side Effects Rating Scale; and Patient-Rated Inventory of Side Effects Scale. A parallel component of the study will involve assaying for baseline language function and the effect of treatment on language using an exploratory acoustic and semantic corpus analysis on recorded interviews. Participant accuracy and response latency on an auditory lexical decision task will also be evaluated.

Methods: We will recruit inpatients and outpatients in the city of Edmonton, Alberta, and will deliver the study interventions at the Grey Nuns and University of Alberta Hospitals. Written informed consent will be obtained from all participants before enrollment. Eligible participants will be randomly assigned, in a double-blinded fashion, to receive active or sham tDCS, and they will continue receiving their usual pharmacotherapy and psychotherapy throughout the trial. In both groups, participants will receive 30 weekday stimulation sessions, each session being 30 minutes in length, with the anode over the left dorsolateral prefrontal cortex and the cathode over the right. Participants in the active group will be stimulated at 2 mA throughout, whereas the sham group will receive only a brief period of stimulation to mimic skin sensations felt in the active group. Measurements will be conducted at regular points throughout the trial and 30 days after trial completion.

Results: The trial has been approved by the University of Alberta Research Ethics Board and is scheduled to commence in June 2021. The target sample size is 60 participants.

Conclusions: This is a protocol for a multicenter, double-blinded, randomized controlled superiority trial comparing active versus sham tDCS in patients with treatment-resistant MDD.

Trial Registration: ClinicalTrials.gov NCT04159012; <http://clinicaltrials.gov/ct2/show/NCT04159012>.

International Registered Report Identifier (IRRID): PRR1-10.2196/22805

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KEYWORDS

neuromodulation; neurostimulation; transcranial direct current stimulation; electrical stimulation therapy; psychiatric somatic therapies; depression; depressive disorder; major depressive disorder; depressive disorder, treatment resistant; randomized controlled trial; therapeutics; clinical trial protocol

Introduction

Depression

As delineated in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, major depressive disorder (MDD) is characterized by the occurrence, and often recurrence, of major depressive episodes [1]. During these times, patients have low mood and/or anhedonia, in addition to at least four other criteria-specific symptoms encompassing emotional, cognitive, and somatic realms, for at least 2 weeks. MDD is a chronic, debilitating mental illness that exerts a profound effect on the quality of life of patients. Taken as a whole, depression is the second highest cause of disability both worldwide and in Canada, with an annual prevalence of 4.3% and a lifetime prevalence of 11.7% [2]. The resultant cost to Canada's economy—from both direct and downstream effects—is a similarly high Can \$32.3 billion (US \$25.6 billion) annually, which is 2% of the nation's gross domestic product [3]. Patients with depression have a 1.5-fold higher mortality rate and a 20-fold higher rate of completed suicide than their nondepressed counterparts [4,5].

Given its immense personal and societal impact, adequate treatment of depressive episodes is of utmost importance. From a physiological perspective, MDD likely arises from an imbalance in the activity of different neuronal circuits, leading to impairments in emotion regulation, social appraisal, cognitive functioning, and a variety of other mental domains [6]. All treatments, be they psychotherapeutic, pharmacological, or neuromodulatory in nature, function by restoring and ideally maintaining balanced neuronal function. Owing to their cost-effectiveness and ease of administration, medication and psychotherapy are first-line treatments for most subtypes of depression; however, 1 in 5 Canadians with MDD are deemed to have treatment-resistant depression that does not adequately respond to either of these modalities [7].

For these patients, the treatment of choice has traditionally consisted of electroconvulsive therapy (ECT), which was first pioneered in 1938 [8]. Although refinements to the procedure have been made since then, the general premise remains the same—by applying a brief, high-intensity electrical stimulus to the brain, one can induce a short seizure that treats depression through a variety of mechanisms [9]. Such treatments are given as a series of 6-16 sessions, in a highly monitored setting, and typically to inpatients in psychiatric facilities. Although effective, this method of neuromodulation has several

limitations. From a health systems standpoint, it is expensive, time consuming, and resource intensive, requiring the services of a psychiatrist, anesthesiologist, and a variety of acute care allied health staff. As such, only specialized facilities routinely offer ECT, which can limit its utility in rural areas. Moreover, it can exert a deleterious effect on the cognitive function of patients during the course of treatment [10]. Even if patients do not experience significant side effects, the requirements of the treatment can impose a high iatrogenic burden. Many individuals are voluntarily hospitalized during their course of ECT, which can last a month or longer and can induce further disruption in their occupational and interpersonal lives. Others still choose not to even pursue ECT owing to their preconceived notions and the high stigma attached to it as a result of its portrayal in popular media [11,12].

Transcranial Direct Current Stimulation

Options for treatment in individuals with refractory depression are limited, especially if they cannot pursue or have had no response to ECT. One promising method of neuromodulation that may be used in this scenario is transcranial direct current stimulation (tDCS). Unlike ECT, which uses a brief, high-intensity stimulus to induce seizures, tDCS consists of the application of a low-intensity current for longer periods (typically 20 to 30 minutes) through electrodes that are applied to the scalp. No seizures are generated, and as such, there is no need for general anesthesia or intensive monitoring; patients may even complete the treatment at home. The device itself, which is fairly simple from a mechanical perspective, is also cost-effective and can be purchased for less than Can \$1000 (US \$790). This compares favorably with ECT and with other neuromodulatory therapies such as repetitive transcranial magnetic stimulation (rTMS), which costs up to Can \$75,000 (US \$59,000) to purchase.

The mechanism by which tDCS exerts its effects is still under study. In part, it may induce long-term potentiation (LTP) and long-term depression (LTD), the mechanisms underlying neural plasticity, in targeted regions of the brain and modulate the activity of neural circuits without generating action potentials. Current flowing out of the anode may induce LTP and increase neuronal activity, whereas current flowing into the cathode may induce LTD and decrease brain activity [13]. Most studies of tDCS in the treatment of depression have applied anodal stimulation over the left dorsolateral prefrontal cortex (DLPFC) and cathodal stimulation over the right DLPFC—areas of the brain which are known to be hypometabolic and hypermetabolic,

respectively, in patients with depression [14]. Due to its targeted nature, tDCS has not been shown to adversely affect cognition and may actually improve cognitive function over the course of treatment [15]. Electrodes can be accurately positioned by surface scalp measurement alone, and neuroimaging-guided localization is not required.

Previous studies have shown that tDCS is a safe and effective treatment for a variety of neuropsychiatric disorders, including schizophrenia, chronic pain, dementia, poststroke rehabilitation, and depression [16,17]. A meta-analysis by Brunoni et al [18], which examined 6 randomized control trials and a total of 289 patients with MDD, found that active tDCS was significantly superior to sham tDCS with respect to both response to treatment (odds ratio [OR] 2.44; number needed to treat [NNT]=7) and the induction of remission (OR 2.38; NNT=9) [18]. These results are similar to those observed for other therapies such as high-frequency rTMS, which has NNTs of 6 and 8 for response and remission, respectively [19].

These results suggest that tDCS may be an effective treatment for MDD; however, its role in treating more refractory cases remains unclear. The meta-analysis by Brunoni et al [18] found that the likelihood of response to tDCS was positively correlated with treatment duration and dose but negatively correlated with treatment resistance (defined as a failure to respond to 2 previous trials of antidepressants). This mirrors the findings seen with other neuromodulation techniques, including ECT and rTMS, and implies that patients with treatment resistance may need to be treated with higher-intensity protocols than their nonresistant counterparts. However, to date, only 3 studies have specifically examined tDCS in patients with treatment-resistant depression, and all have been limited by small sample sizes and relatively low-intensity protocols, among other methodological issues [20-22]. Unsurprisingly, these studies failed to demonstrate the effectiveness of tDCS, yet it remains unclear whether this is truly because of a lack of efficacy or because of issues with study design.

Safety

In a meta-analysis examining over 33,200 sessions of tDCS, no serious adverse events were identified [23]. Common side effects of treatment that occur in up to 50% of patients include mild-to-moderate skin erythema, itchiness, tingling at electrode sites, or mild headache [20,24]. Less commonly observed side effects that have been reported include tinnitus, nervousness, light-headedness, blurred or brighter vision, reduced concentration, nausea, mild euphoria, fatigue, insomnia, or constriction when swallowing. When they occur, these side effects are generally transient and of low intensity.

In patients with bipolar depression, tDCS may rarely induce a manic or hypomanic switch. In a randomized control trial evaluating the use of tDCS in bipolar depression, treatment-emergent affective switches were observed in 15% of patients; however, these did not meet the criteria for hypomanic or manic episodes and did not require hospitalization or treatment discontinuation [25].

Objectives

The main objective of this study is to compare the effectiveness of active versus sham tDCS in ameliorating depressive symptoms in participants with ultratreatment-resistant MDD. We have operationally defined ultrasensitive MDD to include depression that has failed to remit despite the use of ketamine, ECT, or at least five previous antidepressant trials at clinically effective doses. The secondary objectives of the study are to compare the safety of active versus sham tDCS and their respective effects on the speech and language abilities of participants.

Methods

Trial Design

The Neurostimulation of the Brain in Depression (NESBID) trial is a pragmatic, randomized, parallel group, participant- and investigator-blinded multicenter superiority trial. Participants will be randomized in a 1:1 fashion between active and sham tDCS and will continue to receive their usual treatment, including pharmacological and psychological therapies, during the course of the trial.

Eligibility Criteria

All participants will be required to sign an informed consent form before the final determination of their eligibility to enroll in the study. Participants will be eligible for inclusion if they:

- Are adults with a major depressive episode with a score greater than 34 (signifying severe depression) on the Montgomery-Åsberg Depression Rating Scale (MADRS)
- Have ultratreatment-resistant MDD (defined as failure to remit despite adequate trials with 5 antidepressants at clinically effective doses, failure to remit with ECT, or failure to remit with ketamine).

Participants will not be eligible for inclusion if they:

- Are currently diagnosed with psychosis, an addiction disorder (other than nicotine), borderline personality disorder, or antisocial personality disorder, as these conditions could interfere with adherence to the study protocol
- Are currently using a herbal compound or an agent known to modulate NMDA (N-methyl-D-aspartate) receptors, as these substances could interfere with the induction of LTP and thereby limit the effectiveness of tDCS
- Are pregnant, as tDCS has not been adequately studied in this population
- Have an electronic implant, cardiac dysrhythmia, seizure disorder, neurological disorder, or neurosurgical history, as the safety of electrical stimulation with tDCS cannot be assured given these comorbidities.

Participant Recruitment and Randomization

Participants will be recruited from the inpatient population at the Grey Nuns and University of Alberta Hospitals in Edmonton, Alberta. In addition, outpatients in the city and surrounding areas will also be eligible for inclusion. Edmonton is a large and diverse Canadian city, with a metropolitan population of

more than 1.3 million people. Participants may contact the study personnel directly or may be referred by their treating clinician; in the latter case, they must first give consent to disclose contact information to the study coordinators, who will then contact the participant and discuss the trial further. In cases where the treating clinician is also a study coordinator, the informed consent process will occur with a separate coordinator. Participants will be informed that they may withdraw their consent, without penalty, at any time and that this will not affect the care they receive from their treating clinician. Consent cannot be withdrawn after the conclusion of the protocol due to the blinding of participant-identifiable data.

Before randomization, participants will undergo a routine history and physical examination and complete the Edinburgh Handedness Inventory [26]. They will also be interviewed by a member of the research team using the Mini International Neuropsychiatric Interview [27]. This validated, structured tool facilitates the diagnosis of the 17 most common psychiatric pathologies and will provide confirmation that participant diagnoses fall within the acceptable purview of the inclusion and exclusion criteria. Participants will also complete a version of the Massachusetts General Hospital Antidepressant Treatment History Questionnaire, modified with the trade names of Canadian drugs [28]. To ensure that the information obtained is as accurate as possible, research personnel may also augment answers on this scale using historical medication information from a participant's electronic health record. Finally, participants will have their baseline MADRS score recorded to ensure that it is higher than the threshold required for trial participation.

Once the study personnel confirm that participants satisfy the inclusion and exclusion criteria, they will be automatically assigned to a treatment arm using the Research Electronic Data Capture (REDCap) software, hosted at the University of Alberta [29,30]. Randomization will be performed in a permuted block fashion based on a sequence generated by the Robust Randomization App (RRApp) [31]. This sequence will not be known to the study team so as to preserve allocation concealment.

Intervention and Control

In addition to continuing their usual pharmacological and psychological treatments, participants in both arms will receive 30 sessions of either sham or active tDCS, 5 days per week, for a total of 6 weeks, using a Sooma stimulator (Sooma Oy). This constitutes twice the number of treatment sessions as that used in the longest previously conducted study of tDCS in treatment-resistant depression [20]. For both groups, the anode will be positioned over the left DLPFC (position F3 on the 10-20 EEG system), and the cathode will be positioned over the right DLPFC (position F4). Electrodes will be positioned using the caps supplied by Sooma, with participant head circumference measured first to ensure that the proper-sized cap is applied. Each electrode pad will be saturated with 15 mL of normal saline before application.

Participants will be blinded to the group to which they have been assigned. Two stimulators labeled only as *A* and *B* will be set to provide either sham or active stimulation by an investigator not involved in participant interaction or data

collection. In the sham group, the applied current will ramp up from 0.3 mA to 2 mA over 17 seconds and then ramp down to 0.3 mA over 17 seconds, where it will be maintained for the duration of the 30-minute session. Previous trials have demonstrated that this short period of active stimulation is an effective way of triggering scalp tingling at a total dose of tDCS believed to be below the threshold for inducing neuroplasticity changes [32,33]. Current must be maintained at 0.3 mA to allow for operation of the electrode-contact sensors; if these were deactivated entirely, blinding would be broken. In the active intervention group, the applied current will ramp up to 2 mA over 17 seconds and be maintained at that level for 30 minutes, before gradually ramping down.

Participants will be withdrawn from the study if they miss two consecutive treatments or more than five treatments in total, if they undergo a serious adverse event or clinical deterioration (which may include new-onset psychosis, severe suicidal ideation, or a manic or hypomanic switch), or if they or their treating psychiatrist wish them to be withdrawn.

In the unlikely event that a participant undergoes clinical deterioration or that their treating clinician requests their blind be broken, the sole unblinded investigator can be contacted to reveal the treatment code. If the treating clinician is also a study investigator and becomes unblinded as a result of this process, they will be required to recuse themselves from further data collection.

Outcomes

The primary outcome will be the change on the MADRS, a 10-item, validated, observer-administered scale of depression severity, which has been extensively used in trials of depression treatment [34]. Investigators will use a structured interview guide when administering the MADRS to improve inter-rater reliability [35].

Secondary outcomes will include the change on the Quick Inventory of Depressive Symptomatology (QIDS-SR-16), a 16-item, participant-administered scale of depression severity, and the World Health Organization Disability Assessment Schedule (WHODAS 2.0), a 12-item measure of functional impairment [36,37]. Cognitive impacts of treatment will be assessed using the Screen for Cognitive Impairment in Psychiatry (SCIP) [38]. The SCIP has been well validated as a tool for measuring cognitive change in patients with depression and other psychiatric illnesses; is brief and relatively simple to perform; and includes a verbal list learning task, working memory test, verbal fluency test, delayed learning task, and visuomotor tracking test. Exploratory analyses will investigate the effect of treatment on language abilities by change in performance on an auditory lexical decision task, in which participants must differentiate real from fictitious words [39,40]. An exploratory acoustic and semantic corpus analysis will also be conducted on the recorded entrance and exit interviews.

Treatment-related manic or hypomanic switches will be captured using the Young Mania Rating Scale, an 11-item observer-administered scale of mania intensity [41]. Other treatment-related side effects will be measured using a scale derived from a systematic review of tDCS-related adverse events

[42]. This scale has the benefit of asking participants to comment on the relatedness of their symptoms to their treatment and may help to distinguish between the likely side effects of tDCS and symptoms participants had before the intervention. It has also been used in other randomized control trials evaluating tDCS [43]. In addition, side effects that may be secondary to concurrent medication use will be captured using the Frequency, Intensity, and Burden of Side Effects Rating Scale and the Patient-Rated Inventory of Side Effects Scale [44,45]. Side effects captured through the use of the aforementioned scales will be summarized in an adverse events form, with additional documentation completed on any adverse events deemed to be serious in nature.

Data Collection

Measurements for most scales will be conducted at the beginning of the trial (T0), after every 10 sessions (T10, T20, and T30), and 1 month after trial completion (T60; Table 1). Trained psychiatrists, psychiatric residents, and/or medical students will complete all assessments. Data will be collected directly using the REDCap electronic data capture tools.

Recorded entrance and exit interviews will be stored in an encrypted database and have identifying information stripped from them on a rolling basis. This database may then be analyzed in future studies.

Participants will perform the auditory lexical decision task on tablet devices using a previously developed app. They will first answer questions on their age, handedness, native languages, other spoken languages, age at which they began to learn English, English-speaking countries they have visited, and whether or not they grew up in western Canada. They will then hear a series of 200 stimuli and must mark whether they think each stimulus is a real or fictitious word. There are a total of 2000 words split into 32 different lists. Participants will perform this task before commencing treatment (T0), after each stimulation session (T1-30), and 1 month after trial completion (T60).

There are 3 validated versions of the SCIP. To prevent participants from improving their scores by way of repeated exposure, version 1 will be administered at baseline, version 2 after the 30 treatments are delivered, and version 3 at the 1-month postcompletion assessment.

Table 1. Schedule of assessments.

Assessment	Timepoint				
	Enrollment and baseline ^a	Treatment period ^b			Follow-up ^c
	T0	T1-9; T11-19; T21-29	T10; T20	T30	T60
Prerandomization					
Informed consent	✓ ^d	— ^e	—	—	—
Screening of inclusion and exclusion criteria	✓	—	—	—	—
History and physical exam	✓	—	—	—	—
EHI ^f	✓	—	—	—	—
MINI ^g (audio recorded)	✓	—	—	—	—
MGH-ATRQ ^h	✓	—	—	—	—
MADRS ⁱ (audio recorded)	✓	—	—	✓	—
Postrandomization					
MADRS (not recorded)	—	—	✓	—	✓
QIDS-SR-16 ^j	✓	—	✓	✓	✓
WHODAS ^k 2.0	✓	—	✓	✓	✓
SCIP ^l	✓	—	✓	✓	✓
YMRS ^m	✓	—	✓	✓	✓
tDCS-AEQ ⁿ	✓	—	✓	✓	✓
FIBSER ^o	✓	—	✓	✓	✓
PRISE ^p	✓	—	✓	✓	✓
Auditory lexical decision task	✓	✓	✓	✓	✓

^aT0: baseline session.

^bT1-30: treatment sessions 1 to 30.

^cT60: follow-up one session, one month after trial completion.

^dAssessment conducted.

^eAssessment not conducted.

^fEHI: Edinburgh Handedness Inventory.

^gMINI: Mini International Neuropsychiatric Interview.

^hMGH-ATRQ: Massachusetts General Hospital Antidepressant Treatment History Questionnaire.

ⁱMADRS: Montgomery-Åsberg Depression Rating Scale.

^jQIDS-SR-16: Quick Inventory of Depressive Symptomatology.

^kWHODAS: World Health Organization Disability Assessment Schedule.

^lSCIP: Screen for Cognitive Impairment in Psychiatry.

^mYMRS: Young Mania Rating Scale.

ⁿtDCS-AEQ: Transcranial Direct Current Stimulation Adverse Events Questionnaire.

^oFIBSER: Frequency, Intensity, and Burden of Side Effects Rating Scale.

^pPRISE: Patient-Rated Inventory of Side Effects Scale.

Data Analysis and Sample Size Calculations

The primary and secondary efficacy outcomes will be analyzed using a mixed effects repeated measures ANOVA (analysis of variance), with the study group and time as fixed factors and participants as random factors, based on the intention to treat principle. Due to the wide variety of potential adverse events

that can be captured, we will present this information as frequency data.

To detect a moderate effect size for the primary outcome, represented by a Cohen f of 0.25, with a power of 80% and significance $\alpha = .05$, we estimate that 60 participants will need to complete the protocol. This assumes a moderate correlation ($r=0.3$) between time points, using the power curves described in the textbook by Kirk [46]. As a study of this scope, in the

ultraresistant MDD population, has not been performed before, we are unable to estimate the dropout rate. We plan to conduct an interim analysis after 30 participants complete the protocol. We will analyze the main effects of the treatment by presenting the significance of the time, treatment group, and interaction terms in the ANOVA. If there is a significant interaction, we will conduct posthoc comparisons between mean treatment and placebo outcome scores, at each time point, to characterize this effect further and will use the Tukey method to control the familywise error rate.

Results

The trial has received approval from the University of Alberta Research Ethics Board and is registered on ClinicalTrials.gov (NCT04159012). We had planned to begin recruiting participants in 2019; however, all in-person research activities have since been suspended due to the COVID-19 pandemic and its physical-distancing implications. We anticipate that participant recruitment will begin in June 2021 at the Grey Nuns Hospital, with recruitment at the University of Alberta Hospital to begin thereafter. The trial is expected to run until June 2022.

Discussion

Study Overview

In this multicenter, double-blinded, randomized controlled trial, we aim to determine the effectiveness of tDCS in ameliorating ultratreatment-resistant MDD, operationally defined as depression that has failed to remit despite the previous use of at least five antidepressants at effective doses, ketamine, or ECT. In addition to their usual treatment, participants will be randomly assigned to receive either 30 weekday sessions of active (2 mA) or sham tDCS, with the anode over the left DLPFC and the cathode over the right DLPFC. We will regularly assess depression severity and functional impact using the MADRS, QIDS-SR-16, and WHODAS 2.0, throughout the trial and 1 month after study completion. We will assess cognitive changes using the SCIP. We will also regularly assess treatment-related side effects using validated scales.

As depression is known to affect speech [47-49], a parallel component of the study will examine how participant speech and auditory lexical decision changes throughout the trial period. Entrance and exit interviews will be recorded, transcribed (with identifying information removed), and analyzed by collaborators in the Department of Linguistics at the University of Alberta. Participant accuracy and response latency on the auditory lexical decision task will be similarly evaluated and compared.

Strengths

The study has numerous strengths and will follow the CONSORT (Consolidated Standards of Reporting Trials) 2010 statement on design and reporting [50]. Using REDCap to randomly assign participants to treatment groups will ensure that allocation is truly concealed, documented, and

unchangeable. To minimize the placebo effect, both participants and treating investigators will be blinded. Primary and secondary outcomes were chosen to capture a range of subjective, objective, and functional measurements of depression severity, and the regular use of adverse event scales will ensure that treatment side effects are also adequately captured. Measurements will also be taken at multiple points during and after the trial to better describe the overall course and persistence of any treatment-related effects.

This study is unique for several reasons. It is the first of its kind to examine a severely resistant MDD population, in which participants will have failed multiple previous treatments. The use of a relatively intensive tDCS regimen, both in terms of session duration and overall treatment course, is also unique among studies conducted with treatment-resistant patients. To our knowledge, this is also the first study of any therapeutic for MDD that includes detailed measures of language data and function. This may be useful in revealing the effect of tDCS on speech and in building a database of anonymized recordings for use in future analyses.

Limitations

This study also has several practical limitations that may affect the results. With regard to treatment modality, delivering tDCS in a hospital setting will impose a minimal burden on inpatients, but outpatients will have to be functional enough to arrange for transport to the hospital on a daily basis. As such, there is a risk that the study population may miss outpatients with severe depression. The need for daily travel to the hospital can also pose problems with participant compliance. We may use home-based tDCS in future studies to mitigate this, although funding limitations prevented us from employing this approach in the NESBID trial. Second, our blinding procedure follows that used in most other studies of tDCS, but recent evidence suggests that this may not sufficiently mitigate the placebo effect. Turi et al [51] showed that healthy volunteers were able to distinguish the *fade-in, short stimulation, fade-out* method of sham stimulation, described above, from true active stimulation at a level significantly greater than chance. It is not yet known how generalizable these findings are to a population with depression, but there is a need for more research into alternative methods of blinding in tDCS studies.

Conclusions

In conclusion, the NESBID trial is a pragmatic, multicenter, double-blinded study that seeks to compare the impact of active versus sham tDCS in treating ultraresistant depression. To our knowledge, this study is the first of its kind in this patient population and also the first to conjointly employ detailed measures of language function, which will also be used in future analyses. Given the immense health, economic, and societal impacts of MDD, new and effective treatments beyond pharmacotherapy and psychotherapy are needed, and tDCS may prove useful in this regard.

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Conflicts of Interest

None declared.

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Abbreviations

- ANOVA:** analysis of variance
- DLPFC:** dorsolateral prefrontal cortex
- ECT:** electroconvulsive therapy
- LTD:** long-term depression
- LTP:** long-term potentiation
- MADRS:** Montgomery-Åsberg Depression Rating Scale
- MDD:** major depressive disorder
- NESBID:** Neurostimulation of the Brain in Depression
- NNT:** number needed to treat
- QIDS-SR-16:** Quick Inventory of Depressive Symptomatology
- rTMS:** repetitive transcranial magnetic stimulation
- SCIP:** Screen for Cognitive Impairment in Psychiatry
- tDCS:** transcranial direct current stimulation
- WHODAS:** World Health Organization Disability Assessment Schedule

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Protocol

Interprofessional Medication Adherence Program for Patients With Diabetic Kidney Disease: Protocol for a Randomized Controlled and Qualitative Study (PANDIA-IRIS)

Carole Bandiera^{1,2,3}, MSc; Jennifer Dotta-Celio³, PhD; Isabella Locatelli³, PhD; Dina Nobre⁴, NP; Grégoire Wuerzner⁴, MD; Menno Pruijm⁴, MD; Faiza Lamine⁵, MD; Michel Burnier⁴, MD; Anne Zanchi^{4,5*}, MD; Marie Paule Schneider^{1,2*}, PhD

¹School of Pharmaceutical Sciences, University of Geneva, Geneva, Switzerland

²Institute of Pharmaceutical Sciences of Western Switzerland, University of Geneva, University of Lausanne, Geneva, Switzerland

³Center for Primary Care and Public Health (Unisanté), University of Lausanne, Lausanne, Switzerland

⁴Service of Nephrology and Hypertension, Department of Medicine, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

⁵Service of Endocrinology, Diabetes and Metabolism, Department of Medicine, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

*these authors contributed equally

Corresponding Author:

Marie Paule Schneider, PhD

School of Pharmaceutical Sciences

University of Geneva

Rue Michel Servet 1

Geneva, 1211

Switzerland

Phone: 41 22 379 53 16

Email: Marie.Schneider@unige.ch

Abstract

Background: Despite effective treatments, more than 30% of patients with diabetes will present with diabetic kidney disease (DKD) at some point. Patients with DKD are among the most complex as their care is multifactorial and involves different groups of health care providers. Suboptimal adherence to polypharmacy is frequent and contributes to poor outcomes. As self-management is one of the keys to clinical success, structured medication adherence programs are crucial. The PANDIA-IRIS (patients diabétiques et insuffisants rénaux: un programme interdisciplinaire de soutien à l'adhésion thérapeutique) study is based on a routine medication adherence program led by pharmacists.

Objective: The aim of this study is to define the impact of the duration of this medication adherence program on long-term adherence and clinical outcomes in patients with DKD.

Methods: This monocentric adherence program consists of short, repeated motivational interviews focused on patients' medication behaviors combined with the use of electronic monitors containing patients' medications. When patients open the electronic monitor cap to take their medication, the date and hour at each opening are registered. In total, 73 patients are randomized as 1:1 in 2 parallel groups; the adherence program will last 6 months in the first group versus 12 months in the second group. After the intervention phases, patients continue using their electronic monitors for a total of 24 months but without receiving feedback. Electronic monitors and pill counts are used to assess medication adherence. Persistence and implementation will be described using Kaplan-Meier curves and generalized estimating equation multimodeling, respectively. Longitudinal adherence will be presented as the product of persistence and implementation and modeled by generalized estimating equation multimodeling. The evolution of the ADVANCE (Action in Diabetes and Vascular disease: Preterax and Diamicon Modified-Release Controlled Evaluation) and UKPDS (United Kingdom Prospective Diabetes Study) clinical scores based on medication adherence will be analyzed with generalized estimating equation multimodeling. Patients' satisfaction with this study will be assessed through qualitative interviews, which will be transcribed verbatim, coded, and analyzed for the main themes.

Results: This study was approved by the local ethics committee (Vaud, Switzerland) in November 2015. Since then, 2 amendments to the protocol have been approved in June 2017 and October 2019. Patients' recruitment began in April 2016 and ended in

October 2020. This study was introduced to all consecutive eligible patients (n=275). Among them, 73 accepted to participate (26.5%) and 202 (73.5%) refused. Data collection is ongoing and data analysis is planned for 2022.

Conclusions: The PANDIA-IRIS study will provide crucial information about the impact of the medication adherence program on the adherence and clinical outcomes of patients with DKD. Monitoring medication adherence during the postintervention phase is innovative and will shed light on the duration of the intervention on medication adherence.

Trial Registration: Clinicaltrials.gov NCT04190251_PANDIA IRIS; <https://clinicaltrials.gov/ct2/show/NCT04190251>

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KEYWORDS

medication adherence; patient compliance; diabetes mellitus; diabetes complications; diabetic nephropathies; chronic kidney disease; kidney failure; renal insufficiency; electronic monitoring; interprofessional program

Introduction

Currently, approximately 463 million people have been diagnosed with diabetes worldwide [1]. In Switzerland, it is estimated that approximately 500,000 people have diabetes, representing 5.7% of the population [2,3]. Diabetes is associated with a burden of microvascular and macrovascular complications. Diabetic kidney disease (DKD), a microvascular complication of diabetes, affects 30%-40% of the patients with diabetes. Although DKD is the main cause of end-stage renal disease (ESRD), most patients will die of cardiovascular complications before reaching ESRD. Patients with DKD are among the most complex patients receiving diabetes care. Their care is multifactorial and multidisciplinary, involving different groups of health care providers. The multifactorial approach involves pharmacological treatment of various cardiovascular risk factors, including glucose levels, cholesterol levels, and blood pressure levels, and the pharmacological treatment of complications secondary to the reduced renal function. Patients with DKD often take more than 5 daily treatments. Polypharmacy is associated with suboptimal adherence, with risk of an accelerated decline in renal function and ESRD [4]. Although 40% of the patients with DKD do not adhere to their treatments [5,6], literature on medication adherence intervention programs addressing specifically DKD patients is scarce. Recent evaluations showed better metabolic and blood pressure control in patients participating in such programs [7,8]. Furthermore, a high level of self-management, including taking medications, increases the quality of life [6,9]. However, the results of most studies were not conclusive, as medication adherence was evaluated by subjective questionnaires with poor reliability. A feasibility study in patients with DKD who participated in an intervention combining a medication plan and regular phone calls by a specialist nurse did not demonstrate an increase in the medication adherence [10]. Another study concluded that intensive behaviors and interprofessional interventions delayed renal function decline [11]. However, to our knowledge, no study has evaluated the long-term impact of an adherence program or the optimal duration of such a program. It is necessary to better understand the needs of patients with DKD in terms of medication management to achieve better medication adherence and clinical outcomes and slow cardiovascular and renal disease progression.

In 1993, the pharmacy of Unisanté developed an interprofessional medication adherence program (IMAP) to support patients with chronic diseases with their drug management, combining the use of a medication event monitoring system (MEMS and MEMS AS, Aardex Group) and motivational interviews [12]. The first few studies showed encouraging results in improving medication adherence, clinical targets, and retention in care for chronically ill patients [13-18]. The PANDIA-IRIS (patients diabétiques et insuffisants rénaux: un programme interdisciplinaire de soutien à l'adhésion thérapeutique) study is based on this routine medication adherence program led by pharmacists. The global aim of this study is to evaluate the impact of the medication adherence program on long-term adherence and clinical outcomes in patients with DKD.

Methods

Ethical Considerations

The PANDIA-IRIS study was approved by the local ethical committee (Vaud, Switzerland) in November 2015. Since then, 2 amendments to the protocol version 4 have been accepted—in June 2017 and October 2019. This study is being carried out in accordance with the protocol and with the principles of the current version of the Declaration of Helsinki. The results of this study will be submitted to local, national, and international conferences and to a peer-reviewed journal for publication. This protocol has been written according to the SPIRIT reporting guidelines [19].

Objectives

The primary objective of the PANDIA-IRIS study is to assess whether the length of the IMAP (12 vs 6 months) has an impact on medication adherence at 6, 12, 18, and 24 months after enrolment. As a secondary objective, this study will explore whether IMAP intervention changes the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified-Release Controlled Evaluation) [20] and UKPDS (United Kingdom Prospective Diabetes Study) [21] clinical scores of patients with type 2 diabetes at 6, 12, 18, and 24 months after enrolment. Another secondary objective is to explore patient satisfaction with the medication adherence program through 30-minute semistructured qualitative interviews between an investigator and a subgroup of 14 patients included

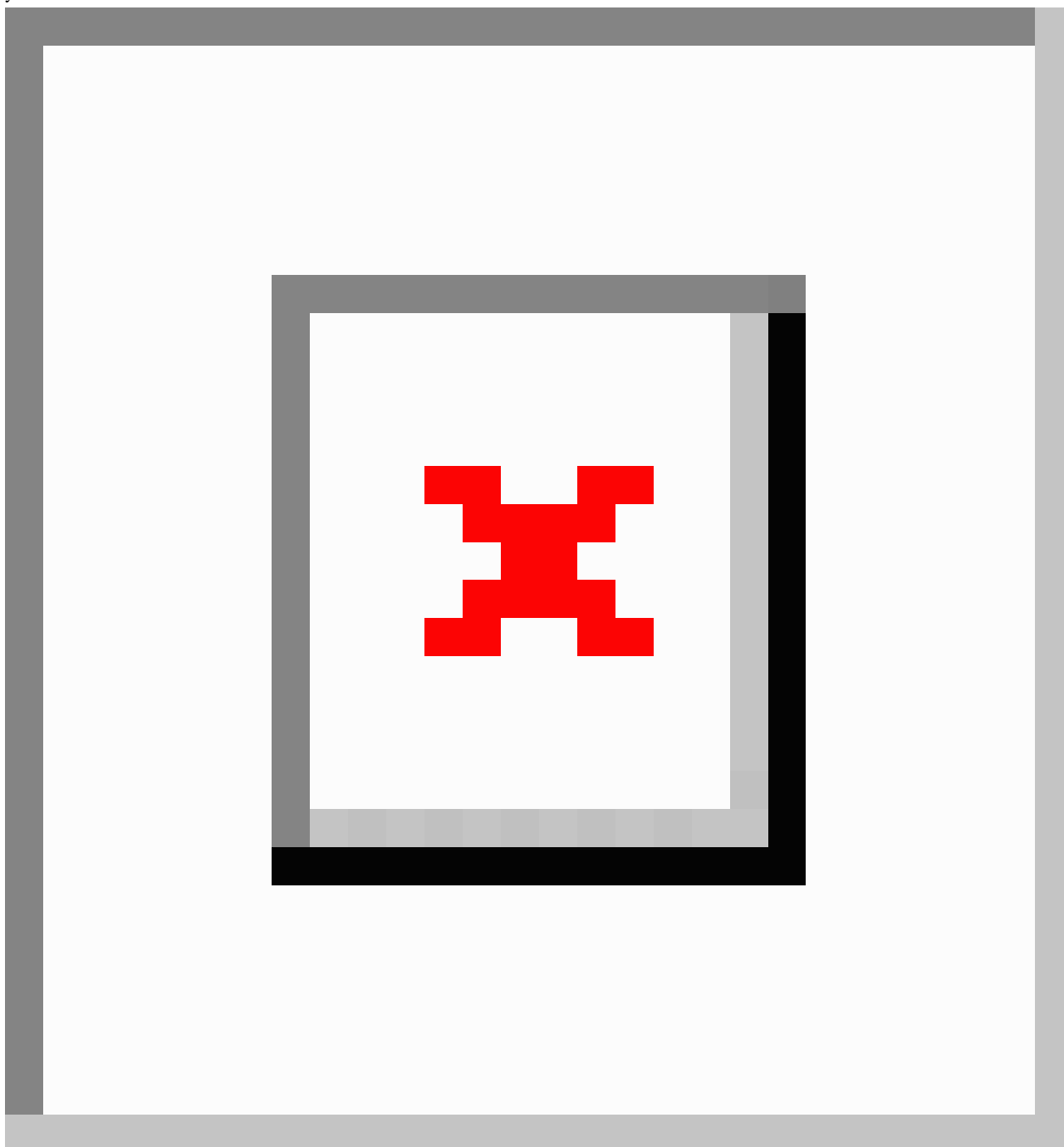
in the PANDIA-IRIS study. The main hypothesis is that patients participating in the 12-month adherence program will have better implementation and persistence, a higher long-term medication adherence rate, and better ADVANCE and UKPDS clinical scores at 12, 18, and 24 months after enrolment than patients in the 6-month intervention group.

Trial Design

The PANDIA-IRIS design uses a mixed approach as it combines (1) a monocentric, prospective, and open randomized controlled

trial and (2) a qualitative study. Patients will be randomized 1:1 in 2 parallel groups; patients of group A will attend the medication adherence program for 12 months and patients randomized to group B will attend the program for 6 months. Satisfaction with this study will be evaluated with selected patients through a qualitative interview at the end of the intervention phase or at the end of this study, or at drop-out (Figure 1). The legend for Figure 1 is available in Multimedia Appendix 1.

Figure 1. Design of the PANDIA-IRIS (Patients diabétiques et insuffisants rénaux: un programme interdisciplinaire de soutien à l'adhésion thérapeutique) study.



Enrolment of the Participants

This monocentric study is being conducted in the diabetes and kidney outpatient clinics in the University Hospital (CHUV, Lausanne, Switzerland), as well as in the outpatient clinic and the University community pharmacy of the Center for Primary Care and Public Health (Unisanté, Lausanne). The PANDIA-IRIS study is voluntary and each patient had to sign an informed consent form to be enrolled. Recruitment began in April 2016 and ended in October 2020. Eligible patients were

identified each week through electronic database screening of all patients with diabetes followed in the University Hospital outpatient clinics. Investigators introduced this study to the eligible patients during a clinical appointment. Recruitment for the qualitative study began in July 2017 and ended in August 2020.

Randomized Controlled Medication Adherence Study

The inclusion and exclusion criteria are presented in [Textbox 1](#) and [Textbox 2](#), respectively.

Textbox 1. Inclusion criteria for the participants.

- Adults older than 18 years who are being followed in the University Hospital and have type 2, type 1, latent autoimmune diabetes in adults, or corticoid-induced diabetes
- One of the following biochemical criteria: estimated glomerular filtration rate (eGFR) ≤ 60 mL/min/1.73 sq m, eGFR > 60 mL/min/1.73 sq m that has decreased > 5 mL/min/year, urine albumin/creatinine ratio > 30 mg/mmol, patients hospitalized at least twice for acute renal impairment in the past 5 years.
- Treatment with at least one of the following drug classes: oral antidiabetic drugs (metformin, dipeptidyl peptidase-IV inhibitors, sodium-glucose cotransporter-2 inhibitors, sulfonylureas, glinides), statins, diuretics, beta-blockers, calcium antagonists, alpha-blockers, angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, or aspirin.
- Fluency in French or English. If not, the presence of an interpreter at each medication adherence visit.
- Full blood test (eGFR, glycated hemoglobin, albumin/creatinine ratio or total, high density lipoprotein and low-density lipoprotein cholesterol) in the 6 months prior to inclusion.

Textbox 2. Exclusion criteria for the participants.

- Incapacity to make decisions, having cognitive disorders, or being under tutelage
- Pregnancy
- Active cancer (not in the remission phase)
- Treatment of the patient is managed by nursing homes or home care services
- Patients already included in an intervention study

All the pharmacists providing the IMAP intervention were trained in motivational interviewing at the University community pharmacy of Unisanté [12]. The technicians were trained in how to complete the electronic monitor data, count pills, and use the MedAmigo software (MEMS and MEMS AS, Aardex Group) to upload electronic monitor adherence data and generate a medication adherence report.

Qualitative Study

Semistructured interviews are conducted with a subgroup of 14 patients included in the PANDIA-IRIS study either at the end of the intervention phase so that the patient remembers the motivational interviews well or at the end of the study so that the patient can discuss the postintervention monitoring phase, or at drop-out. To ensure heterogeneity among the selected patients, patients meeting at least one of the following criteria will be enrolled prospectively: male, female, patients from group A, patients from group B, patients who completed the 24 months of the study, patients who just ended the intervention phase, patients who dropped out, and patients having an adherence rate $> 95\%$ or $< 80\%$.

Intervention

Use of the Electronic Monitor

In both groups, patients use electronic monitors for 24 months. Electronic monitors register the date and hour of each opening, which corresponds to the moment of the drug intake as long as both behaviors are consecutive. Nevertheless, one limitation of this tool is that patients could open the electronic monitor without taking the drug or swallowing it long after the electronic monitor opening. In order to limit this bias and before showing the electronic monitor data to the patient at each pharmacy visit, pharmacists check with the patients that each opening corresponds to the drug intake. They ask the patient about the usual lapse of time between each opening and the real time of the drug intake. The liquid-crystal display (LCD) screen on top of the electronic monitor cap resets at 3 AM each morning. Hence, each time the patient opens the electronic monitor cap, the LCD shows the number of cumulative openings until 3 AM on the next day. The LCD screen reminds the patient about whether the medication has been taken or not.

Drugs to monitor are prioritized based on the following algorithm, which we constructed based on side-effect profiles: (1) all oral antidiabetic drugs, (2) statins, (3) diuretics, (4) beta-blockers, (5) calcium antagonists, (6) alpha-blockers, (7)

angiotensin-converting-enzyme inhibitors, (8) angiotensin II receptor blockers, and (9) aspirin. Moreover, in each class, eligible drugs taken more than once a day prioritize monitoring. The maximum number of monitored drugs is 6. Physicians can modify the treatments at any time. If a patient has to stop all the monitored drugs, he or she will stop the study but the data collected until then will be kept for analysis. If a drug is switched to another eligible drug, the new prescribed drug will be monitored.

Medication Adherence Intervention

All included patients will benefit from the IMAP in addition to routine clinical care. The frequency of IMAP visits is the same in both groups throughout the 24 months: once per month for the first 3 months, followed by 1 visit every 3 months (Figure 1). Pharmacists lead short, repeated semistructured motivational interviews based on the theoretical Fisher model [22]. First, patients' knowledge of treatments is evaluated. Then, motivation to take the treatment, self-efficacy, daily medication behaviors, and side-effect management are explored in an empathetic nonjudgmental way. The graph representing electronic monitor daily openings (dates and hours) since the last visit is shown to the patient as feedback. Adherence results are discussed to reinforce acquired adherent behaviors and to understand nonadherent episodes, and then, solutions with tailored elements are constructed to address nonadherence. To ensure interprofessional collaboration, the pharmacist sends a semistructured report after each medication adherence interview to the clinical team, including the endocrinologist, nephrologist, general practitioner, nurse, dietician, and psychologist. During the COVID-19 pandemic, adherence interviews are conducted through phone calls for some patients, if the clinicians considered them at high risk of complications following infection by SARS-CoV-2. If the interview is conducted by phone, it is notified on the case report form.

Qualitative Study

At the end of the intervention phase or at the end of this study or at drop-out, patients are invited to express their opinions on the medication adherence program and the overall study. Patients who signed the informed consent form specific to the qualitative part of the PANDIA-IRIS study participate in 30-minute in-depth semistructured interviews. The main themes covered are the evaluation of the quality of the medication adherence interview, the positive and negative aspects of the program, the opinions of the patient regarding the electronic monitor, and if the patients completed this study, the perceived impact of the program during the 12-month to 18-month follow-up period.

Postintervention Monitoring Phase

After the intervention phase, patients will still use electronic monitors with their LCD screens, but their adherence data will be double-blinded. Patients will not receive any feedback or motivational interviews about their daily drug management. The clinical team will not obtain any adherence reports. Due to ethical reasons, if the medication adherence rate detected by the MedAmigo software is less than 30% for at least one drug for 2 consecutive pharmacy visits, the software will automatically notify the pharmacist, and the patient will stop

the study and will be oriented to the routine IMAP. If a physician in charge of a patient explicitly asks to access the adherence data during the postintervention monitoring phase for clinically urgent and important reasons, the principal investigator will sign a permission form that will be included in the case report form, and the patient will stop the study. All the data collected until then will be kept for analysis. At 18 months after the inclusion, during the postintervention monitoring phase, blood and urine samples will be collected to determine the clinical values at this time point. Indeed, the frequency of blood and urine samples collection differs between patients, and collecting laboratory values for each patient at this precise time point will ensure consistency in the analysis.

Assignment of Interventions

Patients are randomized 1:1 at inclusion to either the 12-month or 6-month intervention group. According to the risk of nonadherence due to the adverse effects of statins or the complexity of the drug regimen, 4 randomization groups were created: patients treated with statins, patients who have to take at least one drug more than once daily, patients with both of the former conditions, and patients with none of the former conditions. Then, the randomization is performed in each strata and is coded with 0, corresponding to group A, where patients receive the intervention for 12 months, or 1, corresponding to group B, where patients receive the intervention for 6 months. The randomization code is generated by a random repetition of 4 and 6 blocks composed of 1 or 0 (Excel, Microsoft) to prevent predictability of the sequence. The randomization sheets were created by an independent researcher from the Unisanté Research Support Unit. The allocation is established for each consecutive patient by unsealing the randomization sheet. This study is open, and the clinical team as well as the patients are aware of the allocation group.

Outcomes

Primary Outcomes

The global adherence outcome is defined as the percentage of days a patient correctly takes the medication across the individual study duration. The mean global adherence will be compared between groups. According to the EMERGE (ESPACOMP Medication Adherence Reporting Guidelines), medication behaviors will also be described longitudinally in both groups through 3 operational definitions: implementation, persistence, and longitudinal adherence at 6, 12, 18, and 24 months after enrolment [23].

Secondary Outcomes

The ADVANCE and UKPDS clinical scores will be assessed and compared at baseline, 6, 12, 18, and 24 months after enrolment for patients with type 2 diabetes in both groups. The ADVANCE score indicates the risk of developing cardiac complications associated with type 2 diabetes within 4 years and estimates the risk of developing renal complications within 5 years or more than 5 years. The UKPDS score calculates the risk of fatal coronary heart disease or stroke in patients with type 2 diabetes with no antecedent cardiovascular disease. These scores are calculated on the following parameters: sex, ethnicity, smoking status, time since diabetes diagnosis, blood pressure,

glycated hemoglobin, total and high-density lipoprotein cholesterol, atrial fibrillation, albumin in urine, abdominal circumference, and BMI [24].

During the postintervention monitoring phase, the number of patients with less than 30% adherence for at least one drug during 2 consecutive visits as well as the time-to-event will be compared between the groups. We will also describe implementation and persistence at 6 months and 12 months after the end of the intervention in both groups to explore the impact of the length of the intervention on adherence. Patient satisfaction regarding the program will be analyzed through qualitative interviews.

Sample Size

An expert committee composed of nephrologists, endocrinologists, nurses, pharmacists, and statisticians agreed that the difference in the mean global adherence between groups should be 5%. The hypothesis states that the adherence rate will average 97.5% in the 12-month intervention group and 92.5% in the 6-month intervention group. A standard deviation of 1.7 was assumed in the logit scale in both groups. This corresponds to 95% global adherence in the intervals (57.5%-99.9%) and (30.0%-99.7%) for the 12-month intervention group and the 6-month intervention group, respectively. According to these parameters, a sample size calculation was made simulating individual series of daily medication (1=at least the correct number of daily openings of the electronic monitor for all drugs monitored; 0=fewer daily openings than prescribed for at least one drug monitored), in order to consider both the interindividual variability (SD 1.7) and the intraindividual variability (the measurement error). Considering that the mean number of measures of a subject will be 365, 72 patients must be included in this study (36 participants in each group) to have a power of 80% and a two-tailed alpha error of .05. Regarding the qualitative study, the expert committee agreed that a subgroup of 14 included patients will attend the qualitative interview but more patients may be included if data saturation is not reached after the completion of 14 interviews.

Participant Timeline and Data Collection

Data collection is performed by the investigators and is prospectively registered in the platform Research Electronic Data Capture (RedCap), a secure web app for building databases. Each patient has a unique study number generated by RedCap. First, during recruitment, if eligible patients refuse to participate, their reasons for doing so are recorded. For patients included in this study, their sociodemographic data are provided by the administrative software of the hospital at inclusion. Clinical data for each visit are provided by the patient electronic clinical file (Soarian, Cerner) and reported in the case report form. The participant timeline and data collection process are shown in [Multimedia Appendix 2](#) [25] for both groups. Electronic monitor data are uploaded on the secured MedAmigo web portal at each medication adherence visit during the intervention and at each medication refill during the follow-up for both groups. Concomitantly, the patient's electronic monitor use is systematically checked by the pharmacist through a set of validation questions (ie, identification of nonmonitored periods, eg, during hospitalizations, whether medication was sometimes

prepared in advance for a later use since the last visit). A pill count is performed by the technician during the intervention phase and by a blinded independent researcher during the postintervention monitoring phase. The participants who leave this study before completion are not replaced and are considered as dropouts but the data collected until then will be kept for analysis. The data monitoring committee is composed of the main investigators of the PANDIA-IRIS study. After the end of this study analysis, data will be archived and kept for 10 years in the secure data warehouse of the University Hospital before destruction. The database of the PANDIA-IRIS study will be shared in a secured data repository of the University of Geneva (Yareta) at the end of the analysis.

Data Analysis

Sociodemographic and Clinical Data

Sociodemographic and clinical data will be presented as percentages, means, and standard deviations or medians and interquartile ranges depending on the distribution of the data.

Medication Adherence

All dates and the timing of electronic monitor activation will be used to analyze medication adherence. Electronic monitor data will be reconciled with pill counts and patient reports [26]. The global adherence will be calculated as the percentage of days during which the drug is taken properly across the individual study duration. Two-sided Student *t* test will be used to compare the mean probabilities between groups in the logit scale. A difference between groups will be considered statistically significant if $P < .05$. Medication behaviors are characterized by implementation, persistence, and longitudinal adherence [27].

Implementation evaluates at each day the proportion of patients taking at least the correct dose prescribed on that day among the patients who are still participating in the program. For each participant, the daily medication behaviors will be described with a binary variable (1=at least the correct number of daily openings of the electronic monitor for all drugs monitored; 0=fewer daily openings than prescribed for at least one drug monitored). This code is commonly used and cannot discriminate overadherence, which will be considered as adherence. Implementation will be modeled with the generalized estimating equation multimodeling [28].

Persistence corresponds to the distribution of times between inclusion in the study and discontinuation (ie, unilateral stopping of treatment by the patient). Persistence will be described with a Kaplan-Meier survival curve. The log rank test will be used to compare the persistence between groups [28].

Longitudinal adherence is defined at each day as the proportion of patients taking at least the correct dose prescribed on that day among all the patients included in the study. Longitudinal adherence will be presented as the product of persistence and implementation and modeled by generalized estimating equation multimodeling [28]. In an exploratory analysis, univariable and multivariable regressions will analyze the associations among medication behaviors (combining persistence and implementation), sociodemographic and clinical

data at inclusion, and changes in the clinical and biochemical variables at the completion of the study.

The number of patients with adherence rates less than 30% in the postintervention monitoring phase for at least one drug during 2 consecutive pharmacy visits will be compared between groups with a chi-squared test or with Fisher exact test if the sample size is less than 5 patients. The statistician who will perform the analysis will not be aware of the group allocation until the data are completely frozen. Statistical analysis will be performed with the R statistical package (version 3.6, The R Foundation for Statistical Computing) [29].

ADVANCE and UKPDS Clinical Scores

The changes in the ADVANCE and UKPDS scores during the 24-month study will be analyzed with generalized estimating equation multimodeling, considering collected covariables such as sociodemographic data, monitored treatments, and medication adherence.

Qualitative Study

Audio recordings will be transcribed verbatim, and a content analysis will be performed using MAXQDA (VERBI GmbH) software. The codes will be labeled and categorized into themes. To ensure the codification validity, 2 investigators will codify the verbatim transcription independently and discrepancies will be discussed.

Missing Data

Missing data will be clearly identified in the results tables and will not be computerized.

Patient and Public Involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research. Once the results of the PANDIA-IRIS study will be published, the included patients will be informed about the results through a summary flyer using lay language.

Results

Patients' recruitment began in April 2016, ended in October 2020, and it was a challenging task. Indeed, this study was introduced to all consecutive eligible patients (n=275). In total, 73 out of 275 patients accepted to participate (26.5%) and 202 (73.5%) patients refused. Most patients who refused to participate argued that they had developed satisfactory skills and habits in drug self-management over time and that this study would disturb their routine. For instance, most patients already used a weekly pill organizer and were not ready to replace it with electronic monitors. Nevertheless, investigators could not confirm that these patients had no adherence issue. A new quantitative and qualitative substudy has been planned to understand the sociodemographic and clinical variables that differ between the patients who accepted versus those who refused to participate. Qualitative interviews will be conducted

with a representative number of patients who refused to participate to understand their personal reasons for nonparticipation in order to further improve the routine IMAP. Patient recruitment is completed, and sociodemographic and clinical data are prospectively collected for the included patients until October 2022. Data analysis will be performed and results will be submitted for publication in a peer-reviewed open access journal.

Discussion

Strengths of This Study

The PANDIA-IRIS study is the first study to analyze the impact of a pharmacist-led adherence program on long-term medication adherence and cardiovascular scores in patients with diabetes and renal impairment. This study is based on a robust methodology; patients use electronic monitors, often considered as close to the gold standard to assess medication adherence. Moreover, patients are included in the routine IMAP that already led to significant improvements in the medication adherence and clinical outcomes of other chronically ill patients [12,17,18]. The mixed methodology is another strength of this study; the qualitative satisfaction interviews led with a representative number of included patients will enable the research and pharmacy teams together to further adapt the program to the specific needs of patients having DKD.

Limitations

This study has some limitations. First, patients are included for 24 months in this study, which is a relatively long period of time, thereby increasing the probability of change in regimen over time and dropouts. In addition, the adherence data analysis is complex as patients use more than 1 electronic monitor. However, complex medication adherence data analysis was previously developed by the investigators, and the statistician who will perform the analysis is an expert in this field. Secondly, we cannot exclude the Hawthorne effect during the first 6 weeks of this study, explained by the fact that participants might improve their usual medication adherence behaviors as they feel observed [30]. We will analyze adherence as a trajectory (longitudinal, repeated measures) and we will pay attention to this risk during our analysis. All limitations and their possible impacts on the results will be clearly depicted in the final publication.

Conclusion

The PANDIA-IRIS study will provide crucial information about the impact of the medication adherence program on adherence and the clinical outcomes of the patients with DKD who are known for polypharmacy challenges and who are engaged in complex and multifactorial care. Monitoring medication adherence during the postintervention phase is innovative in this field. This analysis will help health care providers to better support medication adherence in patients with DKD.

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Authors' Contributions

CB wrote the manuscript. MS and AZ reviewed it. IL reviewed the statistical part of the protocol. All authors contributed to the elaboration of this study protocol and to the final manuscript. CB, JDC, DN, FL, MP, GW, and MB identified and followed the patients clinically. This work is supported by a grant from SantéSuisse/Curafutura/PharmaSuisse. The sponsors of the PANDIA-IRIS study are the Lausanne University Hospital and the polyclinic of the Center for Primary Care and Public Health (Unisanté, Lausanne, Switzerland).

Conflicts of Interest

None declared.

Multimedia Appendix 1

Caption of the design of the PANDIA-IRIS study.

[PNG File, 60 KB - [resprot_v10i3e25966_app1.png](#)]

Multimedia Appendix 2

Schedule of enrollment, interventions, and data collection for the PANDIA-IRIS study.

[DOCX File, 19 KB - [resprot_v10i3e25966_app2.docx](#)]

Multimedia Appendix 3

CONSORT-eHEALTH checklist (V1.6.1).

[PDF File (Adobe PDF File), 525 KB - [resprot_v10i3e25966_app3.pdf](#)]

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Abbreviations

ADVANCE: Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified-Release Controlled Evaluation

DKD: diabetic kidney disease

ESRD: end-stage renal disease

IMAP: interprofessional medication adherence program

LCD: liquid-crystal display

MEMS: medication event monitoring system

PANDIA-IRIS: Patients diabétiques et insuffisants rénaux: un programme interdisciplinaire de soutien à l'adhésion thérapeutique

RedCap: research electronic data capture

UKPDS: United Kingdom Prospective Diabetes Study

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Protocol

Effects of a School-Based Physical Activity Intervention for Obesity and Health-Related Physical Fitness in Adolescents With Intellectual Disability: Protocol for a Randomized Controlled Trial

Aiwei Wang¹, MPhil; Yang Gao^{1,2}, PhD; Jingjing Wang³, PhD; Tomas K Tong¹, PhD; Yan Sun¹, MSc; Siyue Yu⁴, MPH; Hong Zhao⁵, BEd; Daozhi Zou⁵, BEd; Ziheng Zhang⁶, BEd; Yuling Qi⁷, BEd; Nan Zuo⁸, BEd; Danran Bu^{1,9}, MPhil; Dexing Zhang⁴, PhD; Yaojie Xie¹⁰, PhD; Julien S Baker^{1,2}, PhD

¹Department of Sport, Physical Education and Health, Hong Kong Baptist University, Hong Kong, China

²Centre for Health and Exercise Science Research, Hong Kong Baptist University, Hong Kong, China

³Mass Sports Research Center, Institute of Sport Science, Beijing, China

⁴JC School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong, China

⁵Qianjiang Special Education School, Qianjiang, China

⁶Zhijiang Special Education School, Zhijiang, China

⁷Dangyang Special Education School, Dangyang, China

⁸Yingshan Special Education School, Yingshan, China

⁹HuBei Institute of Sport Science, Wuhan, China

¹⁰School of Nursing, Faculty of Health and Social Science, The Hong Kong Polytechnic University, Hong Kong, China

Corresponding Author:

Yang Gao, PhD

Department of Sport, Physical Education and Health

Hong Kong Baptist University

AAB 927 Academic and Administration Building

15 Baptist University Road

Hong Kong

China

Phone: 852 34113082

Email: gaoyang@hkbu.edu.hk

Abstract

Background: Childhood obesity accompanied by lower levels of health-related physical fitness (HRPF) is a major threat to public health both internationally and locally. Children with intellectual disability, especially adolescents, have a higher risk of being overweight/obese and having poor HRPF levels. Therefore, more interventions are needed to help this population attain their optimal health levels. However, there has been relatively limited research on this population compared with on their typically developing peers.

Objective: The proposed study aims to fill this knowledge gap by developing and examining the success of a physical activity (PA) intervention for the target population.

Methods: The proposed study will be a 12-week, school-based randomized controlled trial. The participants (N=48) will be recruited from special schools for students with mild intellectual disability and then randomly allocated to either the intervention group (IG) or the wait-list control group (CG). During the intervention period, the participants in the IG will receive a fun game-based moderate-to-vigorous PA (MVPA) training program (2 sessions/week, 60 minutes/session, for a total of 24 sessions). The intensity of the activities will increase in a progressive manner. Participants in the CG will receive no program during the study period, but the same PA program will be provided to them after the completion of the study. To observe and evaluate the sustaining effects of the intervention, follow-up testing will be scheduled for the participants 12 weeks after the intervention concludes. The study outcomes will include primary outcomes (obesity- and fitness-related outcomes) and a secondary outcome (blood pressure). All of the measurements will be taken at 3 time points. After the follow-up tests, the same PA training program will be provided to the participants in the CG.

Results: This study is ongoing. The participants were recruited from October 2020 to November 2020. The total duration of the study is 13 months. Study results are expected at the end of 2021.

Conclusions: The proposed study is expected to reduce obesity and improve HRPF levels in children with intellectual disability. If proven effective, the intervention will be made accessible to more special schools and mainstream schools with students with intellectual disability. Furthermore, the study can serve as an example for international researchers, policy makers, and members of the public who are seeking to tackle the problem of obesity and poor HRPF among children with intellectual disability.

Trial Registration: ClinicalTrials.gov NCT04554355; <https://www.clinicaltrials.gov/ct2/show/NCT04554355>

International Registered Report Identifier (IRRID): PRR1-10.2196/25838

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KEYWORDS

children; intellectual disability; physical activity; overweight; obesity; intervention

Introduction

Childhood obesity accompanied with lower levels of health-related physical fitness (HRPF) is a major threat to public health internationally and locally [1]. The global prevalence of overweight and obesity among children has risen dramatically from 4% in 1975 to over 18% in 2016 [2]. This rising trend has been recorded in a wide range of countries [3]. For example, in the United States, obesity prevalence increased from 13.5% in 1995 to 18.5% in 2016 [2]. In China, the prevalence of overweight and obesity increased from 1.1% in 1985 to 20.4% in 2014 [4]. In terms of HRPF levels, the most update-to-date data showed that only 42% to 46% of children had adequate cardiopulmonary fitness (CPF) [5]. Studies have also demonstrated a global decline in CPF levels of 0.36% per year [6]. There is clear evidence that childhood obesity accompanied with lower levels of HRPF leads to short- and long-term risks, including cardiovascular diseases, metabolic syndrome, osteoporosis, type 2 diabetes, hypertension, and certain types of cancer [7,8].

Children with intellectual disability, who account for approximately 1% of the entire pediatric population, are more vulnerable than their typically developing (TD) peers to obesity and lower levels of HRPF [9,10], as they tend to be less active and less empowered to choose and adopt healthy behaviors [3]. The global prevalence of overweight and obesity in children with intellectual disability is 30% to 33% [9], and the risk of developing overweight and obesity is 1.54 to 1.80 times higher in adolescent children with intellectual disability (aged 12 to 18 years) than in their TD peers [3]. In terms of HRPF levels, a cross-sectional study found that 71% to 91% of children with intellectual disability (aged 12 to 18 years) scored below the reference values (for TD children) in CPF and muscular fitness [11].

Therefore, given the high prevalence of obesity and poor HRPF levels, children with intellectual disability, especially adolescents, should be a target population for reducing obesity and improving HRPF levels. Compared with the large body of research on effective interventions for obesity and lower levels of HRPF among TD children, few efforts have been made to examine the effectiveness of interventions for children with intellectual disability. To date, 3 reviews have examined intervention effects on changes in body weight and/or HRPF

levels [12-14] in this population. Harris et al [12] examined the effects of 6 physical activity (PA) interventions that were described as including aerobic and resistance activities. However, no significant effects were found on any obesity-related outcomes. The second review, by Mañano et al [13], focused on lifestyle interventions, including PA, diet, health education, and cognitive behavioral strategies. The review of 9 studies concluded that interventions involving PA were effective in reducing body weight, BMI, fat mass, and peak oxygen consumption per unit time/peak power, and increasing peak power, maximal upper and lower limb strength, and number of sit-ups. However, inconsistent results were found for body fat percentage, waist circumference, and peak heart rate [13]. A third review [14] examined the effects of 6 interventions for excessive weight among children with intellectual disability. The intervention approaches included PA and parental engagement. However, no consistent results were found for any of the intervention types.

Based on the 3 reviews, we cannot draw any firm conclusions on intervention effects because of the limited number of studies involved. In addition, the most recent of the 3 reviews was published in 2014. Since 2014, there has been an increase in the number of interventions in the target population. Therefore, an updated review on the topic is needed to identify effective interventions for this population.

Hence, given the above evidence, we conducted a systematic review and meta-analysis on this topic (data have not yet been published). Our findings suggested the following: (1) PA was the predominant component to be adopted into interventions, with 27 of the 29 identified interventions implementing PA; (2) PA contributes to improving CPF (50.50 m, 95% CI 22.23-78.77; $P<.001$), lower limb muscular strength (19.41 kg, 95% CI 11.32-27.49; $P<.001$), and upper limb muscular strength (4.42 kg, 95% CI 0.12-8.73; $P=0.04$) in children with intellectual disability; and (3) the limited research related to this population prevented us from drawing any confirmed conclusions on relationships with obesity.

In relation to the above, we would like to develop a PA intervention to reduce obesity and improve HRPF levels in adolescents with intellectual disability. The proposed study will be a 12-week, school-based PA program with a 2-armed randomized controlled trial (RCT) design. The primary outcomes will be obesity- and HRPF-related outcomes. Blood

pressure will be evaluated as a secondary outcome, as some common noncommunicable diseases, such as hypertension and diabetes, that occur in adulthood have become more prevalent in children, mainly due to unhealthy lifestyles and obesity [15]. The objectives of the proposed study are to evaluate the effectiveness of the intervention on obesity- and HRPF-related outcomes (primary outcomes) and blood pressure (secondary outcome) and to evaluate sustainable effects of the intervention on all outcomes, with a comparison with a control group (CG) and adjusted for confounding factors (eg, sociodemographic and lifestyle factors).

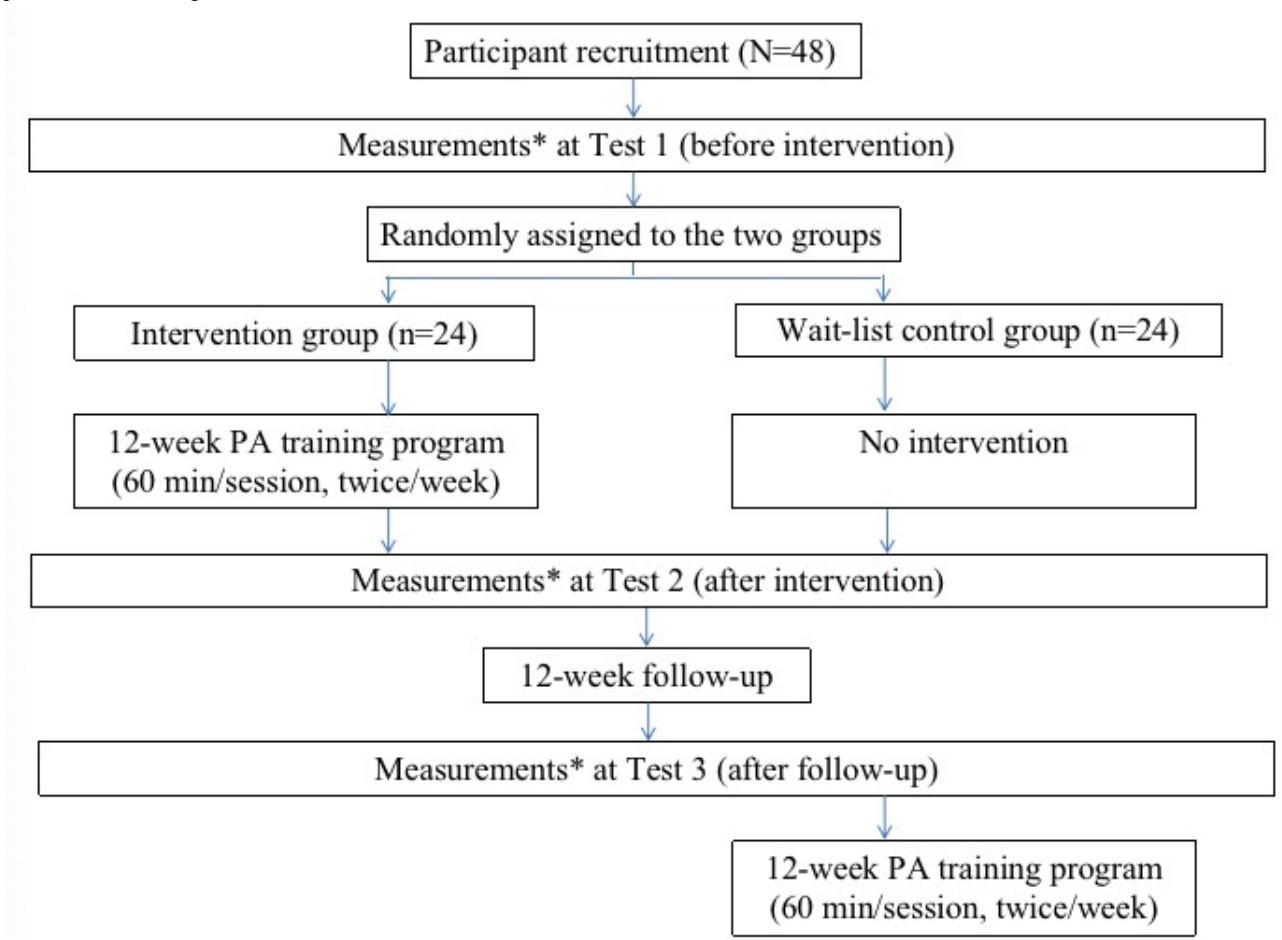
Methods

Study Design

The proposed study will be a 12-week, school-based RCT (Figure 1) that will take place in the Chinese mainland. The participants will be recruited from special schools for students with mild intellectual disability and then randomly allocated to either the intervention group (IG) or the wait-list CG. During the 12 consecutive weeks of the study, the participants in the

IG will receive a fun game-based moderate-to-vigorous PA (MVPA) training program (2 sessions/week, 60 minutes/session, for a total of 24 sessions). The intensity of the activities will increase in a progressive manner. Those in the CG will receive no intervention. All of the participants (in both groups) will be asked to maintain their regular activities during the intervention period. To observe and evaluate the sustaining effects of the intervention, follow-up testing will be scheduled for all of the participants 12 weeks after the intervention ends. The follow-up period of 12 weeks has been chosen to fit the regular school calendar of the local special schools. The study outcomes will include primary outcomes (obesity- and fitness-related outcomes) and a secondary outcome (blood pressure). In addition, control variables including sociodemographic factors, subjective PA levels, screen time, eating habits, and sleep duration will be collected using a questionnaire. All of the measurements will be taken at 3 time points: Test 1 (T1, before the intervention), Test 2 (T2, immediately following the intervention), and Test 3 (T3, after the 12-week follow-up period). After the follow-up tests, the same PA training program will be provided to the participants in the CG.

Figure 1. Flow diagram of the study. *Measurements at Tests 1, 2, and 3 will include obesity- and fitness-related outcomes (primary outcomes), blood pressure (secondary outcome), and confounding variables (including demographic information, subjective physical activity [PA] levels, screen time, sleep duration, and eating habits).



Study Population

Target Population and Selection Criteria

The target population of the study will be overweight and obese students aged 12 to 18 years in special schools for those with mild intellectual disability. Overweight and obesity will be defined according to commonly used age- and gender-specific BMI cutoff points ([Multimedia Appendix 1](#)) [16]. Participants will be selected according to the following inclusion criteria: (1) children with mild intellectual disability; (2) aged 12 to 18 years; (3) overweight or obese; and (4) at least one family member who is able to attend the program with the participant. The exclusion criteria will be children (1) with a physical disability; (2) with a medical predisposition toward obesity (such as genetic syndrome) that could interfere with the results of the study; (3) with contraindications for PA (eg, severe heart disease); or (4) who participated in other obesity- or fitness-related programs in the past 6 months. This research proposal has been reviewed and approved by the Research Ethics Committee of Hong Kong Baptist University.

Sample Size Estimation

The sample size will be calculated using G*Power software (version 3.1.9.4). Previous research has shown that a medium effect size of 0.21 is appropriate [17]. Setting a significance level of $P < .05$, a power level of 80%, and a constant correlation of 0.5, and assuming a 20% dropout rate, a total sample size of 48 participants (24 participants in each group) will be needed.

Participant Recruitment

Invitation letters will be sent to special schools in China. If a school agrees to participate, the physical education (PE) teachers at that school will be contacted to help with the initial recruitment of participants by sending a screening questionnaire to their students to determine if they meet the eligibility criteria for study participation. A written informed consent form will be attached to the screening questionnaire to obtain parental consent in advance. Next, the heights and weights of all eligible participants will be objectively measured at their home school. A BMI will be calculated for each student, and students of normal weight will be removed from the list of potential participants. The recruitment will continue until the estimated sample size ($n=48$) is reached.

Randomization and Blindness

We will randomly and equally assign the 48 participants to the IG and CG using block randomization [18]. The random allocation sequence will be computer-generated by a blinded statistician outside of the research team. Masking of participants will be achieved by the wait-list design, where participants assigned to the CG will receive the intervention after the study and therefore will not know that they are in the CG.

Furthermore, outcome assessors and statistical analysts will also be masked to the group allocation of the participants.

Strategies to Increase Participation and Decrease Dropouts

Previous intervention studies have indicated that parents might refuse to participate if their children do not receive the interventions and thus do not reap the potential benefits of the interventions. To address this issue, we will adopt the wait-list CG design to ensure that all participants will have an equal chance to undertake the PA training program. The PA training program will be free to the participants, and a 100 Chinese Yuan (US \$15.45) coupon will be rewarded to the parent of each participant, which will help to increase participation. In addition, the potential health benefits of the project, such as helping participants decrease body weight and improve HRF levels, will be clearly described to the participants and their parents to increase their interest in participating.

To reduce dropout rates, rewards (eg, stickers) will be given to participants who complete each intervention session. Stationery (eg, pens, erasers) will be given as a reward to participants who achieve an attendance rate of 85% or higher. In addition, only participants who complete the entire study will receive the 100 Chinese Yuan reward, which will also help to reduce withdrawals.

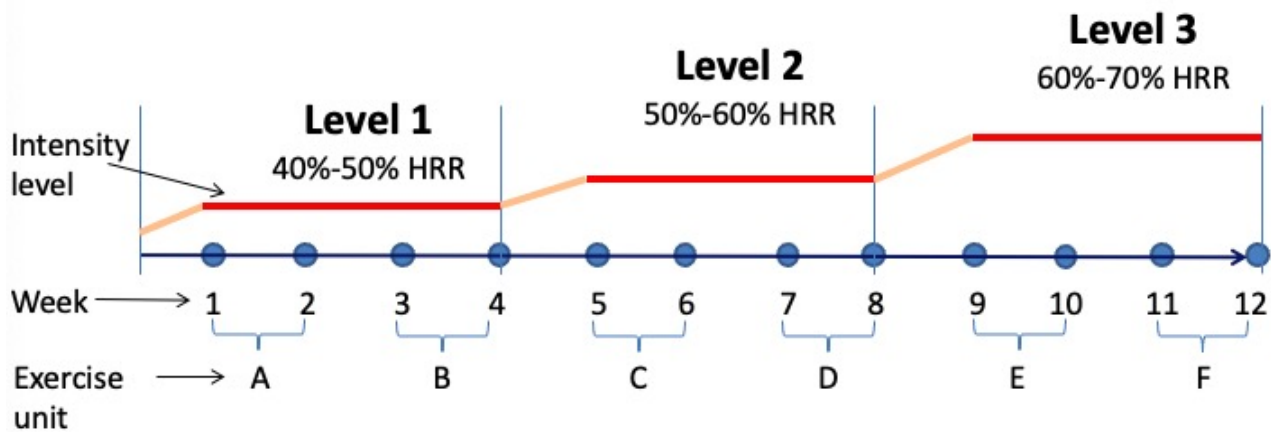
Establishing effective communication channels with parents will increase their confidence in the project. The participants' health status (eg, weight change) and session performance will be reported to their parents by messages upon request. In addition, the participating schools will serve as a communication bridge between the research team and participants/parents. Maintaining strong communication with the schools' PE teachers and nurses will also help the research team to understand the health needs of the participants/parents, which may help to decrease dropout rates.

Description of Intervention

Overview of the Program

The 12-week PA training program will be delivered at a frequency of 2 60-minute sessions per week, with the exercise intensity increasing progressively from 40% heart rate reserve (HRR) to 70% HRR. Each session will consist of both fun game-based aerobic training and resistance training. In addition, the 12-week PA program will be equally divided into 3 levels with different target exercise intensities, and each level will last for 4 weeks. As shown in [Figure 2](#), the target exercise intensity at levels 1, 2, and 3 will be 40%-50% HRR, 50%-60% HRR, and 60%-70% HRR, respectively. In addition, at the beginning of each level, an intensity adaptation period lasting 2 exercise sessions will be given to the participants to help them adapt to the target exercise intensity.

Figure 2. Program overview. HRR: heart rate reserve.



Rationale for Developing the PA Program

The program was designed specifically for children with intellectual disability based on international PA guidelines, exercise guidelines, and evidence from previous PA interventions. The following paragraphs introduce the rationale of the design, including the choice of intervention period, frequency, intensity, time, and content of the proposed program.

Intervention Period: 12 Weeks

A duration of 12 weeks has generally been recognized as necessary for an effective PA training intervention [19]; the results of our systematic review of intervention studies for decreasing body weight and improving HRRPF levels among children with intellectual disability support this selection. Moreover, attrition rates are lower in short-term interventions than in long-term ones [20]. School activities are usually scheduled on a semester basis, and the most commonly adopted length of time of most school activities is 12 weeks. After reviewing local school calendars, we decided that a short-term period of 12 weeks was the most feasible and practical for implementing the intervention.

Frequency: 2 Sessions/Week

Our systematic review revealed that most studies delivered PA training at frequencies of either 2 sessions/week ($n=11$ [21-31]) or 3 sessions/week ($n=9$ [25,32-39]). Elmahgoub et al [25] explicitly compared the 2 frequencies and reported that both significantly improved health outcomes. No significant differences in the effects were found between the 2 intervention arms, except for in lower limb muscular strength, which was better in the 3 sessions/week arm. However, the participants' motivation tended to decline at the end of the program in the arm with 3 sessions/week [25]. As a result, a frequency of 2 sessions/week for PA programs for children with intellectual disability will be used.

Intensity: 40%-70% HRR, Progressively Increased

Current PA guidelines [40] suggest that MVPA (40%-89% HRR) provides health benefits to children. However, a high intensity and excessive training load can result in an increased risk of sports injuries, and children with insufficient PA and poor HRRPF levels might have difficulty adopting high exercise intensities in the early training stages [41]. Therefore, a progressively increasing exercise intensity, from moderate intensity to vigorous intensity, will be used to help children with intellectual disability achieve health benefits in a safer and progressive way.

Time: 60 Minutes/Session

The current PA guidelines suggest that 60 minutes of MVPA per session may help children to achieve health benefits [39]. In addition, our systematic review also revealed that PA programs delivered in 60-minute sessions were more likely to be effective.

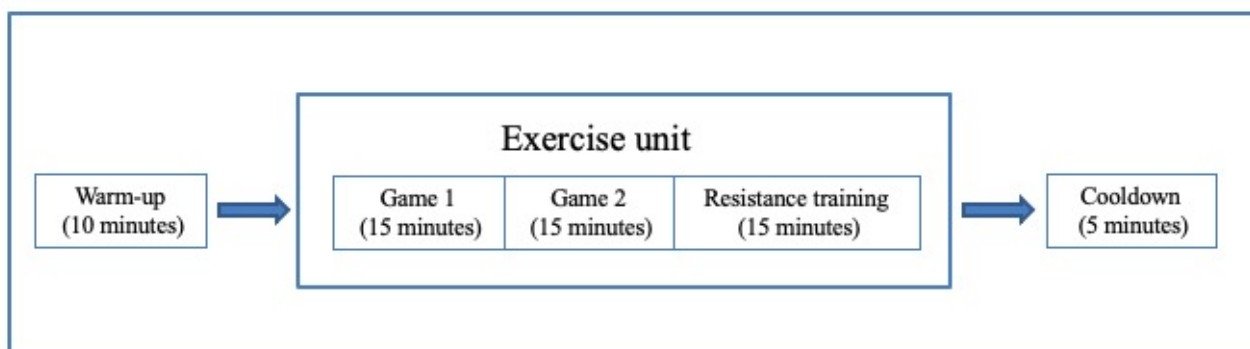
Type: Aerobic Exercise Combined With Resistance Exercise

Evidence from our systematic review suggested that aerobic exercise combined with resistance exercise was the most effective method for reducing obesity [22,25,27,36,42,43] and improving HRRPF levels [25,27,36,38,42,43]. Considering that a fun training mode may improve children's motivation for participation [44], the proposed study will present aerobic exercise in the form of fun games.

Program Content

Detailed Content of Each Exercise Unit

In the program, each training session (see Figure 3) consists of a warm-up (10 minutes), an exercise unit (45 minutes), and a cooldown (5 minutes). Each exercise unit involves 2 different games (15 minutes each) and 3 resistance training exercises (5 minutes each). Each unit will be delivered for 2 continuous weeks. Hence, 6 exercise units with 12 games and 18 resistance training exercises will be prepared.

Figure 3. Structure of a training session.

Content for the 12 games was selected and modified from the Jockey Club Keep-Fit Formula for Children program [45]. Criteria for selection and modification included being (1) safe for children with intellectual disability, (2) easy to learn, (3) fun, (4) able to achieve the intensity requirements, and (5) feasible to perform in special schools. In addition, we have also prepared 6 alternative and replacement games. The resistance training in this program will focus on muscular strength and endurance of children's upper limbs, abdominals, and lower limbs. Self-weight exercises (eg, push-ups, sit-ups, and jumping jacks) will be adopted for resistance training because they are safer to perform than exercises that use fitness equipment.

To improve the operability, rationality, effectiveness, suitability, and feasibility of the training program, the training contents will be evaluated by two experts before implementation, considering their vast experience in related areas. The experts will consist of a PE teacher in a local special school with more than 5 years of working experience and an active researcher in the research areas of body weight control and/or physical fitness training for at least 5 years. The two experts will be invited to provide their evaluations in terms of feasibility, effectiveness, and suitability of program content. Effectiveness here refers to the content of games and resistance training exercises that will

be able to decrease body weight and improve HRF levels; suitability refers to the training content that will be suitable for the participants to perform without harmful effects; and feasibility refers to the training program that will be able to be practiced in school settings. Two rounds of evaluation will be conducted. The first round will be implemented to gather detailed opinions about each exercise unit from experts using a 5-point Likert scale (ie, 1=very weak, 2=weak, 3=neutral, 4=good, 5=very good); the experts will also be required to provide comments or suggestions for any item with a score of less than 4. After completing the first-round evaluation, modifications will be conducted according to the experts' opinions and suggestions. If there are any disagreements or queries/confusion about their opinions, a confirmation letter will be sent to them with appropriate explanations. The second-round evaluation refers to the experts' final evaluation, in which they will be required to give their final assessment of each exercise unit as a pass or fail (scores ≥ 4 indicate a pass and scores < 4 indicate a fail) [46].

Table 1 summarizes the selected and backup games and resistance training exercises. Multimedia Appendices 2 to 7 present the details of exercise units A to F, and Multimedia Appendix 8 presents the six back-up games.

Table 1. Details of the exercise units.

Weeks	Exercise unit	Main games and backup games ^a	Resistance training exercises ^b
1-2	A	<ul style="list-style-type: none"> 1. I'm a Tigger 2. Watch me: dribbling and layup (1)^b Backup 1: Cross the tunnel 	Handgrips (1); jumping jacks (1); sit-ups (1)
3-4	B	<ul style="list-style-type: none"> 1. Jump, jump, throw 2. Tomb robbing Backup 2: Caterpillar 	Push-ups (1); squats (1); burpees (1)
5-6	C	<ul style="list-style-type: none"> 1. Cross the river together 2. Obstacle competition (1)^b Backup 3: Flip color disks 	Handgrips (2); jumping jacks (2); sit-ups (2)
7-8	D	<ul style="list-style-type: none"> 1. Watch me: dribbling and layup (2)^b 2. Rapid team (1)^b Backup 4: Reaction by color disk 	Push-ups (2); squats (2); burpees (2)
9-10	E	<ul style="list-style-type: none"> 1. Step jumping 2. Rapid team (2)^b Backup 5: Run and kick 	Handgrips (3); jumping jacks (3); sit-ups (3)
11-12	F	<ul style="list-style-type: none"> 1. Obstacle competition (2)^b 2. Funny shuttle run Backup 6: Dodgeball 	Push-ups (3); squats (3); burpees (3)

^aSee [Multimedia Appendix 8](#) for a detailed description of backup games.

^bThe number in parentheses indicates the level of the game or exercise.

Intensity Monitoring and Control

To ensure that the participants' exercise intensity level reaches the target requirements, we will calculate their target exercise heart rate (HR) using equations 1 to 3 in [Textbox 1](#) [47]. Resting heart rate (HR_{rest}) will be measured using an automated device (Omron M6 [HEM-7000-E]; Omron Corporation) at the beginning of each training level. Maximal heart rate (HR_{max}) will be estimated using equation 3 in [Textbox 1](#). In each training session, participants' real-time exercise HR will be calculated

two times by tutors by counting the number of beats on their wrists for 10 seconds and then multiplying by six. If the real-time exercise HR is lower than the lower limit of the target range, appropriate modifications (eg, encouraging them to run faster or jump higher) will be adopted to improve their exercise intensity (see [Multimedia Appendices 2 to 7](#)). If the exercise HR is higher than the target range's upper limit, appropriate modifications (eg, encouraging them to run slower or take a rest) will be implemented as well.

Textbox 1. Equations for calculating target exercise heart rate (HR) [47].

Equations

1. Target exercise HR (beats/min) = target % × heart rate reserve (HRR) + resting heart rate (HR_{rest})
2. HRR (beats/min) = maximal heart rate (HR_{max}) – HR_{rest}
3. HR_{max}(beats/min) = 210 – 0.56 × age (in years) – 15.5 × (2 [for children with Down syndrome] or 1 [for children without Down syndrome])

The required exercise intensity for each exercise unit must be estimated. Exercise units with predicted lower intensity will be placed at the beginning of the program (eg, level 1). Over time, the required exercise intensity will increase. The intensity of each exercise unit can be controlled by adjusting the running distance, movement speed, or duration of rest intervals. Specific methods for controlling the intensity of each exercise are given in [Multimedia Appendices 2 to 7](#).

Safety Assurance

In each training session, the ratio of tutor to participant will be 1:3. Hence, there will be enough tutors to ensure the participants' safety. The tutors will pay close attention to participants' exercise performance to prevent sports injuries. In addition, all of the games are from the game series promoted by the Hong Kong Physical Fitness Association. They are recognized as safer than most self-designed games. As different exercise units may have different characteristics, the safety procedures will vary according to the exercises (see [Multimedia](#)

Appendices 2 to 7). Furthermore, the equipment used in the program will not have sharp edges. It is better to choose equipment that the participants are familiar with or often used in their PE classes. Moreover, drinking times will be arranged in each training session (eg, participants will drink water every 20 minutes). Finally, in case of emergency, at least one PE teacher from each participant school will be required to attend and assist with each exercise session and on-site data collection.

Program Delivery

Location

The PA training programs will be conducted in the participants' schools. A fixed sports area in each participating school, such as a basketball court or the indoor activity venue, will be necessary.

Training Time Arrangement

The training program session will be scheduled in a non-PE class time slot during school hours. It will be discussed with each participant school.

Ratio of PA Instructors to Participants

To ensure that the participants receive individualized instruction but also have interaction opportunities with their peers [48,49], the proposed study will have a high tutor to participant ratio of at least 1:3 for each training session.

PA Instructor Recruitment and Training

The tutors should have some knowledge of PE and have experience leading PE courses for students with special needs. Three training sessions (60 minutes per session) will be provided to all tutors. During the sessions, we will explain the background, objectives, and significance of the study and the characteristics of the participants. Then, we will introduce the interventions and the methods for exercise intensity control and safety for each exercise unit. Finally, all of the study measurements will be introduced.

Description of Control

Initially, no intervention will be delivered to the participants in the CG during the intervention period. Also, they will not be permitted to join any other related programs. They will be asked to continue their usual school activities. All participants in the CG are expected to receive the same PA program after the completion of this study to ensure that they have the same opportunity to improve their health.

Measures

Obesity- and fitness-related outcomes will be measured as the primary outcomes. Blood pressure will be a secondary outcome. The participants' demographic information will be collected at baseline and used as a control in data analysis. Moreover, other potential confounders, such as subjective PA level, screen time, sleep duration, eating habits, and pubertal stage, will also be collected and used as controls in data analysis. All of the measurements, except the demographic data, will be collected at baseline (T1), postintervention (T2), and at the 12-week follow-up (T3). A set of evaluation instruments has been drafted.

Primary Outcomes

Obesity-Related Outcomes

Body Weight

Body weight will be measured with a Tanita body composition analyzer (TBF-410), which is accurate to 0.1 kg. The scale will be cleared before each participant is weighed, and the participants will be asked to look straight ahead and stay still until the digital screen settles before the measurement is recorded. The data reliability can be further increased by using the same scale to measure all of the participants. Body weight will be measured at 3 time points and treated as a continuous variable. Changes in body weight, as an obesity-related outcome, will be calculated and compared between the IG and CG.

BMI

BMI scores will be calculated as weight divided by the square of height (ie, kg/m^2). Measurement of weight is described in the section above. Height will be measured using a height gauge accurate to 0.1 cm (Harpenden Stadiometer, Holtain Ltd). When measuring heights, the participants will be asked to remove their shoes and stand straight, with knees and feet together. BMI will be evaluated at 3 time points and treated as a continuous variable. Changes in BMI, as an obesity-related outcome, will be calculated and compared between the IG and CG. BMI is also a categorical variable, which will be used for overweight and obese classification.

Waist Circumference

Waist circumference will be measured midway between the lowest rib margin and the top of the iliac crest at the end of a gentle expiration [50] using a flexible meter ribbon accurate to 0.1 cm. Waist circumference will be measured at 3 time points and treated as a continuous variable. Changes in waist circumference, as an obesity-related outcome, will be calculated and compared between the IG and CG. Waist circumference will also be used to estimate the waist-to-height ratio.

Hip Circumference

Hip circumference will be measured at the widest part of the body below the waist [51] using a flexible meter ribbon accurate to 0.1 cm. Hip circumference will be measured at 3 time points and treated as a continuous variable. Changes in hip circumference, as an obesity-related outcome, will be calculated and compared between the IG and CG.

Waist-to-Height Ratio

Waist-to-height ratio will be calculated as waist circumference divided by height. It will be evaluated at 3 time points and treated as a continuous variable. Changes in waist-to-height ratio, as an obesity-related outcome, will be calculated and compared between the IG and CG.

Body Fat Percentage

Body fat percentage will be estimated with the Tanita body composition analyzer (TBF-410) using foot-to-foot bioelectrical impedance analysis. After entering the participant's gender, race, height, and age, the participant will be instructed to stand with bare feet on the metal footplates. The data will be displayed automatically. This variable will be estimated at 3 time points

and treated as a continuous variable. Changes in body fat percentage, as an obesity-related outcome, will be calculated and compared between the IG and CG.

Fitness-Related Outcomes

6-Minute Walk Test

The 6-minute walk test will be used to measure participants' CPF. The test has been shown to have acceptable validity and reliability for adolescents and young adults with intellectual disability [52]. Testing procedures will follow the study protocol of Chow et al [53]. Participants will be instructed and encouraged to cover the greatest possible distance on a flat surface 25 m in length. They will be instructed to keep a steady pace, whether running or walking. A trained examiner will measure and record the distance covered by each participant. Each participant will be assigned a trained partner (university student helper) based on the participant's special physical condition and cognitive ability to receive verbal direction and encouragement during the test. The 6-minute walk test will be performed at 3 time points, and the distance covered will be treated as a continuous variable. Changes in distance, as a fitness-related outcome, will be calculated and compared between the IG and CG.

Number of Stands in 30-Second Sit-to-Stand Test

A 30-second sit-to-stand test will be used to assess participants' lower limb strength and endurance. It measures the maximum number of times a participant can rise to a full standing position from a seated position in a 30-second period, without pushing off with their arms. This test is administered using a chair with a seat height of approximately 35.6 cm, without arms. The participants will be instructed to sit with back straight and feet approximately shoulder-width apart and placed on the floor. Arms will be guided to be crossed at the wrists and held against the chest. The number of completed stands will be recorded. This test was first developed for older adults and is highly correlated with strength of the lower limbs [54]. A high correlation of the test score with the strength of the lower limbs ($r=0.69$) has also been found for adolescent children with intellectual disability [33,52]. The number of stands within a 30-second period will be measured at 3 time points and treated as a continuous variable. Changes in the number of stands, as a fitness-related outcome, will be calculated and compared between the IG and CG.

Number of Sit-Ups in 1 Minute

A 1-minute sit-up test will be adopted to evaluate participants' abdominal muscular strength and endurance. The task requires participants to perform as many sit-ups as possible in 1 minute or until the participant experiences muscle fatigue and cannot perform any more. Participants will be instructed to cross their arms on their chests with hands on shoulders, tighten their abdominal muscles, and rise up to touch elbows to thighs. Then, they will return to the start position and repeat [55]. The number of sit-ups completed in 1 minute will be measured at 3 time points and treated as a continuous variable. Changes in the number of sit-ups, as a fitness-related outcome, will be calculated and compared between the IG and CG.

Handgrip Strength

The handgrip strength test will be used to assess participants' hand and forearm muscular strength. During the test, the participant will be instructed to adopt a standing position with arms at his/her side, not touching the body. The participant will be asked to squeeze the instrument with as much force as possible for 10-20 seconds. Right and left hands will be alternated [36]. Handgrip strength will be measured at 3 time points and treated as a continuous variable. Changes in handgrip strength, as a fitness-related outcome, will be calculated and compared between the IG and CG.

Sit-and-Reach Distance

For the sit-and-reach test, each participant will begin by removing his/her shoes and sitting down at the test apparatus. One leg will be fully extended with the foot flat against the end of the testing instrument. The other knee will be bent, with the sole of the foot flat on the floor 5 cm to 8 cm to the side of the straight knee. The arms will be extended forward over the measuring scale with hands palms down, one on top of the other. Each participant will be instructed to reach directly forward with both hands along the scale 4 times and to hold the position of the fourth reach for at least 1 second. After measuring one side, the participant will be asked to switch the position of his/her legs and reach again [55]. The distance of the sit and reach will be measured at 3 time points and treated as a continuous variable. Changes in the distance of the sit and reach, as a fitness-related outcome, will be calculated and compared between the IG and CG.

Secondary Outcome

Blood Pressure

The participants' systolic and diastolic blood pressure will be measured using an Omron blood pressure monitor (calibrated before using). During the test, the participant will be asked to sit quietly for approximately 5 minutes and then remove outer garments and roll up their shirtsleeves, if necessary, to bare the upper right arm. The measurements will be taken on the right arm. The participant's arm will be resting on the desk so that the antecubital fossa is at the level of the heart, with the palm relaxed and facing upward. Then, the cuff will be placed on the right arm, with the bottom edge 1 cm to 2 cm above the antecubital fossa. The top edge of the cuff cannot be restricted by clothing. Two measurements will be taken 1 minute apart, and the readings will be recorded. Before and during the measurement, it is necessary for the participant to be calm [56]. Blood pressure will be measured at 3 time points and treated as a continuous variable. Changes in blood pressure will be calculated and compared between the IG and CG.

Confounding Variables

Subjective Measurements of PA Level, Screen Time, Sleep Duration, Eating Habits, and Pubertal Stage

Subjective data on participants' PA level, screen time, sleep duration, eating habits, and pubertal stage will be collected using a self-report questionnaire. As the participants may not be able to fully understand questionnaires independently, the participants and their parents will complete the questionnaire together at

home. In addition, to increase the reliability of the responses regarding participants' school activities and snacks, a short version of the self-report questionnaire will be administered to the participant's schoolteacher. Subjective PA level, screen time, sleep duration, eating habits, and pubertal stage will be collected at 3 time points and treated as confounding variables. They will be used as controls in the data analysis.

The Chinese version of the Global Physical Activity Questionnaire (GPAQ) will be modified to estimate participants' PA and sedentary behaviors. The modified GPAQ will contain 12 items to ask about the frequencies and duration of moderate and vigorous PA in school, transport, and leisure time situations in a typical week. There will be 2 additional questions about sedentary behaviors in a typical week. Furthermore, we will add questions about screen time (2 items) and sleep duration (2 items) on a typical weekday and on weekends. The average daily time spent performing MVPA will be calculated for the participants and used to divide them into 2 groups (active versus inactive) based on the PA level for children recommended by the World Health Organization (ie, 60 minutes/day). For sedentary behaviors, a cutoff point of 4 hours/day will be adopted to distinguish the 2 groups. The average sleep duration will also be used to divide the participants into 2 groups (sufficient versus insufficient, with a cutoff point of 8 hours/day) [57].

Questions about participants' eating habits will be adapted from a dietary questionnaire developed by the Central Health Education Unit of Hong Kong for school-aged children [58]. The questionnaire will feature 9 items to evaluate the frequency of food consumption, including the consumption of fruits, vegetables, meats, fish, eggs, beans, grains, fried foods, sweetened drinks, high-sugar foods, high-salt foods, and high-fat foods. The questionnaire will also include 4 items to measure eating habits at breakfast and dinner. In addition, we have adopted questions about snacks (3 items) and fast foods (1 item) from a dietary questionnaire for children that was developed by the Pennsylvania Department of Health [59].

Puberty is a dynamic process of development marked by rapid changes in body composition and health outcomes [60]. Adolescents of the same age may differ in the rate of their physical growth [61]. Research suggests that Tanner staging from a clinical assessment is the gold standard measurement of puberty status [61]. The Tanner staging system consists of 5 stages, separately designed for boys and girls, which are determined by pubic hair growth in both sexes, breast development in girls, and testicular development in boys [62]. However, this kind of assessment is challenging in school settings. As a result, the self-assessment of puberty status might be more acceptable to the participants [60]. In this study, an illustrated Tanner pubertal questionnaire will be provided to participants to collect the information regarding pubertal stage [63].

Process Evaluation

Process evaluation will be used to monitor and document the implementation of the intervention [61]. A framework model for designing a process evaluation of RCTs will be adopted. Participants' retention rate, adherence rate, and compliance to

the intervention will be assessed. Moreover, all participants will be asked about their satisfaction with the intervention, perceived effectiveness and usefulness of the intervention, future participation intention, and intention to recommend the intervention to others in a 5-point Likert scale questionnaire [64].

Quality Control

Manual and operational procedures will be prepared for all of the team members. Three training sessions (60 minutes/session) will be provided. Monthly and ad hoc research meetings with experts (university teachers) in the PA area, student helpers, and PE teachers/nurses in the special schools will be held to ensure the success of the proposed study. To promote a uniformly high performance, we will conduct unannounced quality assurance inspections (2 times/month) in the field. The data will be checked by auditors immediately and entered twice to enhance accuracy. Moreover, on the written informed consent form, we will request that the participants in the IG and their parents do not communicate with any parents and classmates in the school about the intervention to avoid contamination and behavioral spillover. In addition, we will seek the participating schools' help to remind them and monitor and prevent occurrences of such behavior.

Data Collection Procedure

Once participants have been recruited, informed consent forms and questionnaires will be sent to the participants. They will be completed by the parents with the assistance of the participants within 1 week and returned to their schoolteachers. To ensure the confidentiality of the personal information, these files will be sealed in an envelope. The parents of the participants who do not send back the forms will be contacted via a phone call or text message. New documents will be prepared and sent to the parents if the documents have been lost or mislaid.

After collecting the required documents, we will arrange a morning session to conduct the obesity- and fitness-related tests and blood pressure measures for the participants. The test procedure is as follows: heart rate test and blood pressure measurement first, then the obesity-related tests, and finally the fitness-related tests. The 6-minute walk will be the last fitness test. If a participant is absent on the test day, another test session will be arranged after consultation with the school.

Data Analysis

SPSS Statistics (version 23.0; IBM Corp) will be used for the data analysis. Mean (SD) and/or median (IQR) values will be calculated for the continuous variables (eg, BMI). All of the continuous variables at T1 will be tested for between-group differences using an independent sample *t* test. Normality will be checked using Q-Q plots and tested for equal variance, as assessed by Levene's test. If skewed, the data will be logarithmically transformed before the *t* test is applied. A repeated measures analysis of variance will be used to test for significant differences in the changes in the continuous outcome variables between the 2 groups, where group and time are the 2 factors of interest and will be controlled for significant confounding factors (eg, age). The variables will be selected in a stepwise manner, and only those with $P < .1$ will be kept in the

final models. A significance level of .05 will be adopted (2-tailed test). Intention-to-treat analysis will be adopted and performed to avoid bias from withdrawals or protocol deviations.

Pilot Study

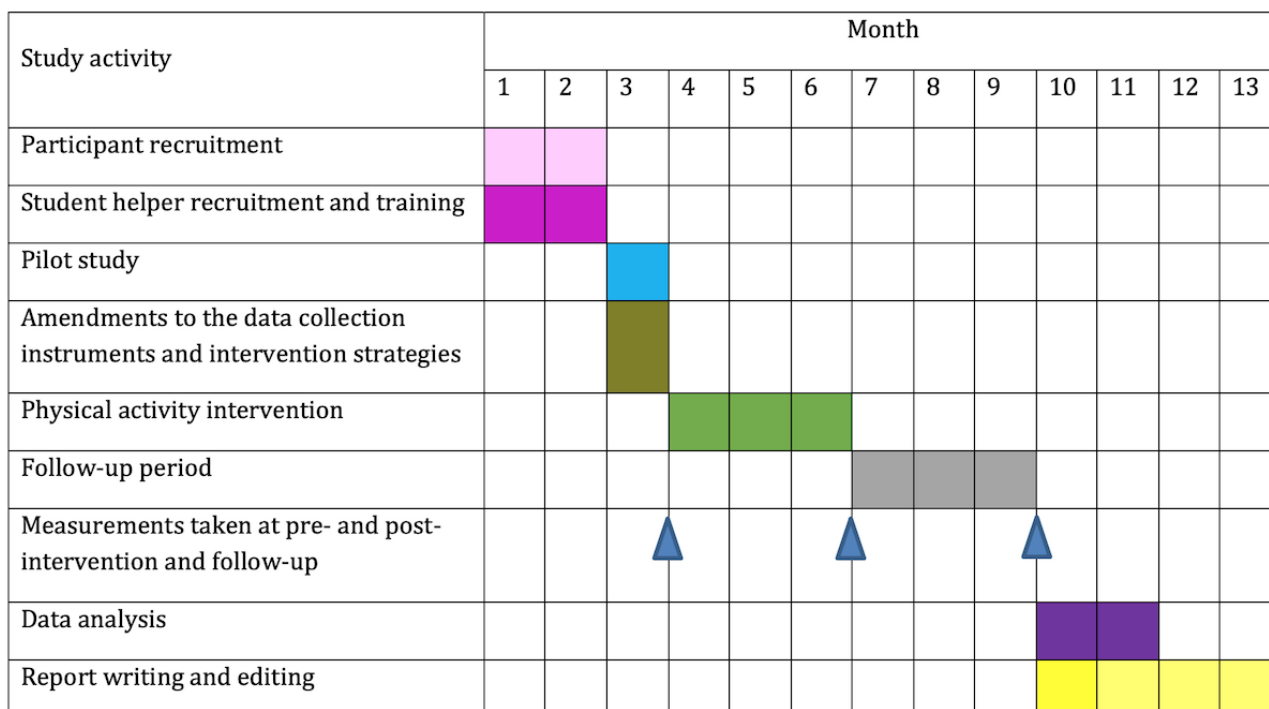
A 2-week pilot study in approximately 10 overweight/obese adolescents with mild intellectual disability will be conducted to test the data collection procedures (outcome measurements) and instruments (questionnaires) and to observe the adaptability of the intervention content. Amendments will be made where necessary. The pilot study will also be used to test the intensity

of the 12 selected games. If necessary, the game order will be changed or some games may be replaced with backup games to meet the intensity requirements. The participants in the pilot study will not be involved in the main study.

Results

This study is ongoing. The participants were recruited from October 2020 to November 2020. Total duration of the study is 13 months. Study results are expected at the end of 2021. Figure 4 shows the timeline of the study (by month).

Figure 4. Study timeline.



Discussion

Childhood obesity accompanied with lower levels of HRPf is a major threat to public health both internationally and locally [1]. Children with intellectual disability, especially adolescents, have a higher risk of being overweight/obese and having lower levels of HRPf [9,57]. Therefore, more interventions are needed to help this population attain its optimal health. However, there has been relatively limited research on this population compared with on its TD peers. The proposed PA program will address this knowledge gap by examining the success of the intervention for the target population.

This study has some limitations that need to be acknowledged. First, the PA level is a confounding variable in this study and will be collected in the form of self-reporting because most children with intellectual disability refuse to wear accelerometers, according to our previous experience. Self-reporting methods may result in problems in capturing accurate PA levels. Future studies, therefore, should consider ways to obtain PA levels from children with intellectual disability as accurately as possible. Second, results of this study cannot be applied to children with severe or profound intellectual

disability because there may be possible differences associated with different levels of intellectual disability. Third, results of this study may not be applied to children studying in mainstream schools, as school settings between special schools and mainstream schools may be different.

One of the strengths of this study, in our view, is that the PA program was developed based on the results of our systematic review and meta-analysis, which was used to identify effective lifestyle interventions for reducing obesity and/or improving HRPf levels in children with intellectual disability. Other strengths of this study include the use of fun games to improve children’s motivation for participation [44]. To our knowledge, this is the first time that fun games have been adopted to tackle the target health problems in children with intellectual disability. To improve the rationality, suitability, and operability of this program, the contents of the fun games and resistance exercises will be evaluated by experts before implementation, using their vast experience in the related areas. Moreover, the RCT design with sufficient sample size, detailed inclusion and exclusion criteria, and standardized testing may improve the research quality.

If proven effective against obesity and poor HRPF, the intervention design will be made available to the participating special schools so that the intervention can continue to benefit their students. If successful, the program will also be promoted to other local special schools with students with intellectual disability. Furthermore, the study can serve as an example for

international researchers, policy makers, and members of the public who are seeking to tackle the problem of obesity and poor HRPF among children with intellectual disability. The aim is to ultimately eliminate the existing health inequities between children with intellectual disability and their TD peers.

Acknowledgments

We initially planned to implement the intervention in Hong Kong, China, but because of the COVID-19 pandemic, all special schools have suspended their on-campus activities since April 2020, with no plan/timetable for reopening. Given that the COVID-19 situation in Hong Kong is still ongoing, while that in the Chinese mainland has been well-controlled, we will therefore implement the study in the Chinese mainland.

Authors' Contributions

AW and YG wrote the manuscript. AW, YG, JW, and TKT conceived this study. YS, SY, HZ, DZ, ZZ, YQ, NZ, DB, DZ, and YX contributed to the development of the protocol. YG and JSB revised the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

International BMI criteria for overweight and obesity by sex for children between 12 and 18 years old.

[\[DOCX File, 14 KB - resprot_v10i3e25838_app1.docx\]](#)

Multimedia Appendix 2

Details of exercise unit A.

[\[DOCX File, 16 KB - resprot_v10i3e25838_app2.docx\]](#)

Multimedia Appendix 3

Details of exercise unit B.

[\[DOCX File, 16 KB - resprot_v10i3e25838_app3.docx\]](#)

Multimedia Appendix 4

Details of exercise unit C.

[\[DOCX File, 16 KB - resprot_v10i3e25838_app4.docx\]](#)

Multimedia Appendix 5

Details of exercise unit D.

[\[DOCX File, 16 KB - resprot_v10i3e25838_app5.docx\]](#)

Multimedia Appendix 6

Details of exercise unit E.

[\[DOCX File, 16 KB - resprot_v10i3e25838_app6.docx\]](#)

Multimedia Appendix 7

Details of exercise unit F.

[\[DOCX File, 16 KB - resprot_v10i3e25838_app7.docx\]](#)

Multimedia Appendix 8

Details of 6 backup games.

[\[DOCX File, 18 KB - resprot_v10i3e25838_app8.docx\]](#)

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Abbreviations

CG: control group
CPF: cardiopulmonary fitness
GPAQ: Global Physical Activity Questionnaire
HR: heart rate
HRmax: maximal heart rate
HRPF: health-related physical fitness
HRR: heart rate reserve
HRrest: resting heart rate
IG: intervention group
MVPA: moderate-to-vigorous physical activity
PA: physical activity
PE: physical education
RCT: randomized controlled trial
TD: typically developing

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Protocol

Community-Integrated Intermediary Care (CIIC) Service Model to Enhance Family-Based, Long-Term Care for Older People: Protocol for a Cluster Randomized Controlled Trial in Thailand

Myo Nyein Aung¹, MBBS, MSc, PhD; Saiyud Moolphate², MPH, PhD; Motoyuki Yuasa^{3,4}, MD, PhD; Thin Nyein Nyein Aung⁴, MBBS, MMedSc, PhD; Yuka Koyanagi⁵, MSc, PhD; Siripen Supakankunti⁶, PhD; Ishtiaq Ahmad⁴, MD, PhD; Ryoma Kayano⁷, MD; Paul Ong⁷, PhD

¹Advanced Research Institute for Health Sciences and Faculty of International Liberal Arts, Juntendo University, Tokyo, Japan

²Department of Public Health, Faculty of Science and Technology, Chiang Mai Rajabhat University, Chiang Mai, Thailand

³Faculty of International Liberal Arts, Juntendo University, Tokyo, Japan

⁴Department of Public Health, Juntendo University, Tokyo, Japan

⁵Tokyo Ariake University of Medical and Health Sciences, Tokyo, Japan

⁶Faculty of Economics, Chulalongkorn University, Bangkok, Thailand

⁷Centre for Health Development, World Health Organisation, Kobe, Japan

Corresponding Author:

Myo Nyein Aung, MBBS, MSc, PhD

Advanced Research Institute for Health Sciences and Faculty of International Liberal Arts

Juntendo University

2-1-1, Hongo, Bunkyo-ku

Tokyo, 113-8421

Japan

Phone: 81 3 3813 3111

Email: dr.myonyeinaung@gmail.com

Abstract

Background: Thailand is one of the most rapidly aging countries in Asia. Traditional family-based care, which has been the basis of most care for older people, is becoming unsustainable as families become smaller. In addition, women tend to be adversely affected as they still form the bulk of caregivers for older people, and many are likely to exit the labor market in order to provide care. Many family caregivers also have no or minimal training, and they may be called upon to provide quite complex care, increasing the proportion of older people receiving suboptimal care if they rely only on informal care that is provided by families and friends. Facing the increasing burden of noncommunicable diseases and age-related morbidity, Thai communities are increasingly in need of community-integrated care models for older persons that can link existing health systems and reduce the burden upon caring families. This need is common to many countries in the Association of Southeast Asian Nations (ASEAN).

Objective: In this study, we aimed to assess the effectiveness of a community-integrated intermediary care (CIIC) model to enhance family-based care for older people.

Methods: This paper describes a cluster randomized controlled trial comprised of 6 intervention clusters and 6 control clusters that aim to recruit 2000 participants in each arm. This research protocol has been approved by the World Health Organization Ethics Review Committee. The intervention clusters will receive an integrated model of care structured around (1) a community respite service, (2) the strengthening of family care capacity, and (3) an exercise program that aims to prevent entry into long-term care for older people. Control group clusters receive usual care (ie, the current system of long-term care common to all provinces in Thailand), consisting principally of a volunteer-assisted home care service. The trial will be conducted over a period of 2 years. The primary outcome is family caregiver burden measured at a 6-month follow-up, as measured by the Caregiver Burden Inventory. Secondary outcomes consist of biopsychosocial indicators including functional ability, as measured using an activity of daily living scale; depression, as measured by the Geriatric Depression Scale; and quality of life of older people, as measured by the EuroQol 5-dimensions 5-levels scale. Intention-to-treat analysis will be followed.

Results: The CIIC facility has been established. Community care prevention programs have been launched at the intervention clusters. Family caregivers are receiving training and assistance. However, the COVID-19 pandemic delayed the intervention.

Conclusions: Since ASEAN and many Asian countries share similar traditional family-based, long-term care systems, the proposed CIIC model and the protocol for its implementation and evaluation may benefit other countries wishing to adopt similar community-integrated care models for older people at risk of needing long-term care.

Trial Registration: Thai Clinical Trials Registry TCTR20190412004; <http://www.thaiclinicaltrials.org/#>

International Registered Report Identifier (IRRID): DERR1-10.2196/20196

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KEYWORDS

aging; Asia; care prevention; health promotion; long-term care; implementation research

Introduction

Background

Thailand's population is estimated to be the third most rapidly aging in the world [1]. While it has a strong health system with a well-established system of universal health coverage, Thailand still needs to develop a long-term care (LTC) system and LTC insurance program. Policies are also needed to sustainably finance an effective LTC model for an estimated 11 million older people in 2020 [2]. Family-based, long-term care (FLTC) is the current model for the majority of LTC in Thailand.

Families form the backbone of the LTC system, a trait that is common to many Southeast Asian countries [3]. However, as families become smaller in Thailand, the sustainability of FLTC is challenged by human resources and its suitability as the technical needs for the care of older people become more complex. Vastly differing levels of education and care competencies found within family caregivers may cause inequalities in the care of older people across lower-resource and lower-income countries [4]. Furthermore, increasing caregivers' burden and opportunity cost pose a key challenge to fast-aging countries where informal care in FLTC is the backbone of aging care. Such burden leads to job loss of the caregivers, abuse of older persons, and caregiver burnout. Interventions promoting the care capacity of informal care in FLTC become essential. Moreover, community-integrated respite service is required to reduce caregivers' burden, sustain FLTC, and promote both older persons' and caregivers' health.

Among the Asian countries except Japan, FLTC is the common choice for most older adults. In some cases, it may be the only choice [3,4]. Recent literature reports studies of LTC models that are well established in high-income countries and compared them to the system of informal family caregiving in many Asian countries such as Thailand [4,5]. Aging and LTC in low-income Asian countries are insufficient for institution-based care and facilities, with policies tilting more towards relying on families and unpaid caregivers. However, many studies reported that FLTC in Asia had a greater positive impact on the psychosocial well-being of older adults [4,6].

In Thailand, as in many Association of Southeast Asian Nations (ASEAN) countries, families, particularly adult children, play

a major role in giving care to older adults [3]. There are challenges to FLTC in the context of the Thai society. Adult children may migrate to work in geographically distant places, and concurrently, the sizes of families are in decline [7,8]. Moreover, the FLTC model prevents women and carers from entering the labor force and can place significant unmitigated burden and stress on those providing care. Based on predictions of increasing burden on family caregivers [6,7] it is important to strengthen the traditional FLTC model by initiating a feasible, formal LTC service and care prevention program.

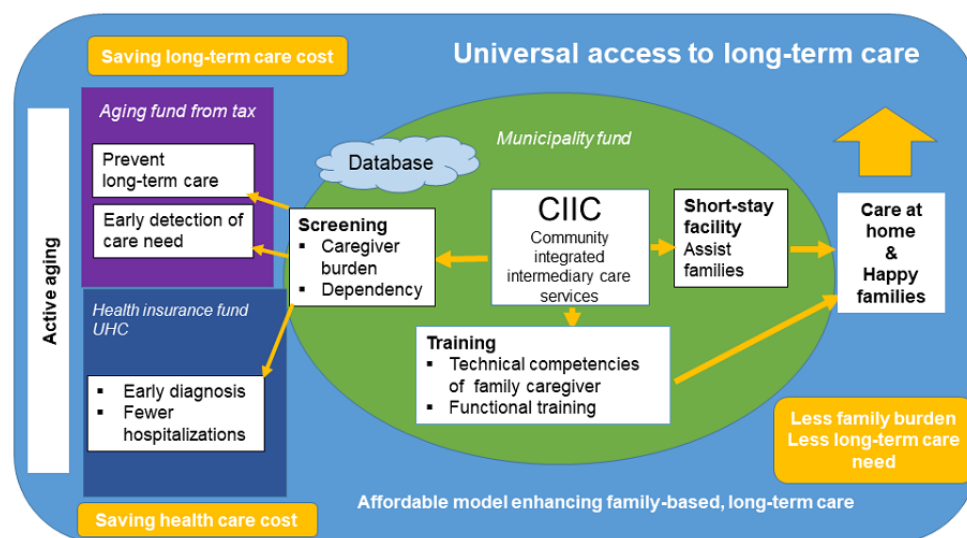
If the weakness in FLTC in terms of technical and professional needs can be strengthened through community-based innovation, the results could be reduced burden of family caregivers, a positive impact on the biopsychosocial outcomes of older adults, and potentially improved healthy aging in communities. Therefore, research assessing the efficacy of innovative LTC models that are contextually relevant is urgently required to assist policymakers who will need to create evidence-based policies to strengthen or build LTC systems including FLTC.

In the context of limited facilities for LTC amidst a growing population of older people, intermediary care models can be an attractive option [9]. A recent study in Australia reported the promising impact of intermediary care centers on reducing family burden and improving the well-being of older adults [10]. This study suggested that intermediary care service with early detection and preventive services may be cost-effective.

Whether the presence of a community-integrated intermediary care center in a district can reduce the burden of family caregivers and promote the functional ability and quality of life (QOL) of older adults in the communities of Thailand is an interesting research question that has not yet been researched systematically. This study aims to assess the efficacy of a community-integrated intermediary care (CIIC) model and compare it to the existing traditional family care model in Thailand.

The CIIC model (Figure 1) is carefully designed to link the existing health care system and services in Thailand to the LTC needs of older people. The screening activity of the CIIC aims to screen for dependency and continually assess family caregiver burden, which could detect early low-level care needs and thereby prevent the future need for more intensive LTC.

Figure 1. Conceptual framework of the Community-Integrated Intermediary Care (CIIC) model for older persons. UHC: universal health coverage scheme.



In Thailand, when environmental alterations are required to accommodate the needs of an older person, such as house management, handrails, and toilet and bathing modifications, district and local municipal funds usually support these needs. If older adults need assistive devices for instrumental activities of daily living (ADL), such as wheelchairs and walking sticks, there is an insurance scheme supported by national taxation (Figure 1). The proposed CIIC service will identify those who are in need and link these older people and their families to existing funds and providers. Moreover, community-based screening activities may identify persons with hypertension, diabetes, and other medical problems. The CIIC team can refer these individuals to the primary health care unit or the community hospital where all Thai citizens can access medical care as part of universal health coverage under the national health insurance program.

Recent policy in Thailand tends to support local governments in setting up centers for aging and LTC through social security insurance. This bill was passed to support municipal governments in the provision of LTC. Additionally, local governments also have their own budgets. However, there is a gap between the FLTC system and its integration with community-based health and LTC services that are managed by local government and municipalities. CIIC is expected to provide a model filling this gap (Figure 1).

Study Hypothesis, Objectives, and Rationale

Hypothesis

Improved competencies of family caregivers may reduce their stress and burden and promote the well-being of older adults as well as increase caregivers' productivity. Functional training exercises for older people will preserve active aging whereas better home care will prevent LTC needs and hospitalization and could decrease health care costs. We hypothesized that there will be differences between the intervention clusters utilizing CIIC services and control clusters in terms of family caregiver burden, functional ability of the older persons, and their QOL.

Such an intervention will be evaluated in a randomized controlled trial, but individual randomization is not realistic and threatens the validity of the results by contamination. Therefore, a clustered randomized controlled design will recruit eligible villages and consented community residents, older persons, within the village as a cluster.

Objectives

This study aims to assess the effectiveness of a CIIC facility and its functions to assist families providing LTC for older adults in terms of reducing caregivers' burden as the primary outcome. Another objective is to evaluate the effectiveness of the CIIC model in terms of the following secondary outcomes: impact on ADL, depression, and QOL of older people.

Methods

Trial Design

This is a 2-arm, parallel-design, interventional study designed as a cluster randomized controlled trial. A total of 4000 participants will be recruited in 12 clusters, 6 in the intervention group with 2000 older adults and 6 in the control group with 2000 older adults in Chiang Mai province, Thailand.

The unit of randomization, cluster, is a village. Participants in intervention clusters will receive the CIIC intervention after screening for eligibility. The eligibility criterion for a cluster is a village that has more than 300 older persons over 60 years of age at the time of randomization.

Inclusion Criteria for Study Participants

The inclusion criteria are >60 years of age, has a family caregiver(s), either male or female, and resident in study site districts.

Exclusion Criteria

People with the following characteristics will be excluded: lack of informed consent by those >60 years old or their family caregivers, cannot understand the explanation for informed consent despite being provided with language support, in a

household without an older person >60 years old, or cognitive impairment or severe impairment of decision-making abilities.

Study Setting

Chiang Mai, Northern Thailand is the location of the study. There are 284,457 older adults in Chiang Mai city according to the 2019 provincial report. Older adults account for 18% of the population, which is higher than the national proportion of people ≥60 years old (16%). Chiang Mai is culturally similar to many neighboring ASEAN countries in terms of caring for older parents as a family tradition and social value.

Two subdistricts involved in the study, sub-district XXX (10 villages) for intervention and subdistrict YYY (15 villages) for control, are in the same Muang Chiang Mai district of Chiang Mai province. They are geographically distant from each other. They have similar demographic and sociocultural characteristics. Both subdistricts have a similarly sized population (>18,000 people), with similar aging rates (>18% of the population is >60 years old), according to local population statistics. People in both subdistricts are mostly Thai people who have access to health care services through the national health insurance system and social welfare services for older people covered by municipality funds.

Intervention

The intervention consists of (1) screening and assessment of family burden and LTC capacity, (2) care capacity building for family caregivers, (3) care prevention and functional training for older adults, and (4) a respite care service for families with caregiving difficulties.

Care in Both Arms

In both arms, a basic health check, blood pressure check, and BMI assessment will be provided for the study participants. If

any disease is suspected through the health check, appropriate referrals to existing health care services will be provided. This is considered a benefit for all study participants. The control group will receive the same assessment with an explanation that the assessment is being conducted as part of a survey and the result will be utilized for research purposes. They also receive the benefit of the additional health check followed by appropriate referrals to health care professionals. Control arm participants will receive usual care (ie, the current system of LTC common to all provinces in Thailand), consisting principally of a volunteer-assisted home care service in addition to traditional family-based home care. The differences between the 2 arms are the newly launched CIIC services, as described in the following sections.

Screening and Assessment of Family Burden and LTC Capacity

After obtaining informed consent, screening of the families will be conducted to assess the capacity for and burden of caregiving for each family with older adults. All older adults and caregivers in each cluster who have provided informed consent will be screened for ADL status and health-related QOL utilizing the EuroQol 5-dimensions 5-levels (EQ-5D-5L) for older adults, and caregiver burden will be measured with the Caregiver Burden Inventory (CBI). The results will be utilized as a baseline assessment from which to measure the overall impact of the CIIC center.

Care Capacity Building for Family Caregivers

Based on the screening, a caregiving capacity building educational program will be provided to the family caregivers of dependent older adults (Table 1), based on the results of a recent study that indicated challenges with FLTC are due to a lack of education and technical competencies of family caregivers [11].

Table 1. Content of the capacity building and training in the Community-Integrated Intermediary Care (CIIC) service model.

Category	Households with dependent older adults	Households with active or less dependent older adults
Whom to train	Family caregiver	Older adults
What to train	Prioritization of conditions for individually tailored care needs	Functional training to preserve functional ability and prevent the need for long-term care
How	Training delivered at home or can be group training, depending on the individual situation and specific care need	Group training 2 times a week as a care prevention exercise program
Who will train	CIIC nurse or assistant	CIIC nurse or assistant or invited experts such as a physical therapist or physical educationist

Care Prevention Exercise Program

Several exercise programs for preventing frailty and LTC will be provided to all the older adults in each intervention cluster (Table 2). The exercise program is based on a recent Japanese study that showed a positive, significant effect with 3 months of training on muscle strength, function, and cognitive [12,13]. A Japanese expert in this training will develop sets of exercises suitable for Thai older adults and train CIIC staff and community volunteers who will then become the trainers in the implementation of the study. Several awareness campaigns to

motivate community older adults to become physically active will be conducted to increase access to the exercise program. Along with the implementation of the training, several physical functions (grip strength, flexibility, functional reach, static balance, walkability, and timed up and go tests) will be measured to assess the effect of the training.

The capability of participants to engage with the exercises will be screened before the training by a doctor or nurse. Blood pressure and heart rate will be measured, and a safety checklist will be completed as part of a safety assessment. Emergency response training or refresher courses such as for the provision

of cardiopulmonary resuscitation and utilization of automated external defibrillator devices will be provided. The maximum size of one training class is 30 people. One session of training will comprise 10 minutes of stretching exercises, 30 minutes of functional training and exercises, followed by 10 minutes of cooling down and stretching. A total of 24 sessions (2 sessions per week for 12 weeks) will be provided.

The 30 minutes of functional training will entail a set of very light exercises for muscle flexibility as well as exercises to improve joint range to help maintain daily mobility and functioning. Very mild resistance training using soft rubber bands (Theraband) will be performed. It aims at maintaining

and improving physical fitness especially for frailer older people and promotes personal exercise habits. This is one strategy for the prevention of the need for LTC.

Care-prevention exercises will be primarily delivered as community group exercise in each cluster in the intervention arm. In addition, participants will be offered an exercise poster, DVD, and safety instruction in order to practice the exercises at home.

In case the intervention proves to be beneficial, caregivers who could not access the study because the older person refused to participate will be informed that they can receive the training if they are still interested.

Table 2. Tentative plan for a Community-Integrated Intermediary Care (CIIC) short-term stay at a respite care facility for older persons.

Type of staff	Number of staff	Function and services
Auxiliary nurses ^a	2	CIIC facility duty; coordination (arranging and scheduling screening and training), technical training of family caregiver for specific care needs, functional training to prevent a need for care
Nurse assistants	2	CIIC facility duty, care of older adults staying at the CIIC (meals, laundry, beds, and personal care), providing technical training for the family caregiver to provide specific care needs
Volunteers	30	Helping with the training of caregivers, social marketing of the CIIC to the community, psychosocial support, assistance with functional training, assisting CIIC staff

^aThese nurses are employed by this research project and are not seconded from the health system.

Respite Care Service for Families Having Difficulties With Caregiving

In this project, intermediary care is defined as formal care that is neither day care nor a long-term residential service. It is a short-term residential service for older persons whose caregiver is temporarily unable to sustain care at home.

Registration

All the families assessed to be eligible for respite care services will be invited to register for the CIIC center's temporary respite care services, which is not part of the primary health care center of the subdistrict. The services will be provided by newly established CIIC centers staffed with professional staff and volunteers who will provide assistance to family caregivers whenever they find it challenging to sustain caregiving of an older family member. The maximum length of stay is 10 days during the 6-month intervention. Our previous survey study found that 6.5% of older persons had decreased capabilities for ADL that required caregiver assistance [11]. Therefore, the estimated number of persons needing respite care is 130 people in a year; 50% (65/130) may be without a caregiver. These individuals will be provided with residential care; therefore, our calculations show that 5 beds would be sufficient for 10 persons at 2 weeks per year. This might not be enough beds during certain periods of the year. Therefore, a booking service will be provided.

Staff

CIIC centers will have 2 auxiliary nurses, 2 nurse assistants, and 30 caregiving volunteers. Auxiliary nurses in Thailand have a bachelor's degree in public health, underwent an internship at primary health care centers, and received accredited advanced training in caregiving that certifies that they have achieved minimum professional standards and technical quality.

Volunteers who received caregiving training will assist the auxiliary nurses.

Applicants

The CIIC temporary respite care service will be provided to applicants with full-time, unpaid family caregivers caring for dependent individuals who are ≥60 years old and meet the eligibility as assessed using the ADL and CBI, as described in the following sections.

ADL Criteria

In order to be eligible to be admitted to the CIIC facility, the family caregiver must be personally providing the care recipient with assistance for at least 2 of the following 6 ADL. The first is bathing: The family caregiver is assisting the older adult with bathing, including help with washing, shampooing, getting in or out of the tub or shower, brushing teeth, and other aspects of personal grooming (Bathing ADL score 0). The second is dressing: The family caregiver is assisting the older adult with dressing, including helping the individual put on or take off clothing and footwear (Dressing ADL score 0 or 1). The third is toileting: The family caregiver is helping the older adult get on or off the toilet, commode, or bedpan as well as clean themselves, or the individual is incontinent (Toileting ADL score 0 or 1). The fourth is transferring: The family caregiver is helping the older adult get to and from a bed or chair (Transfer ADL score 0 or 1). The fifth ADL is walking or mobility: The family caregiver is helping the older adult move from one stationary point to another by removing obstacles, opening doors, and assisting with canes, wheelchairs, or other assistive devices (Mobility ADL score 0 or 1). The sixth is eating or feeding: The family caregiver is helping the older adult who has difficulty chewing or swallowing without assistance or needs partial or total help with eating (Feeding ADL 0 or 1).

CBI Criteria

On the assessment of caregiver burden, the following 2 eligibility criteria are required to utilize the respite care service: time dependency items score >17 and physical health items score >14.

If there is only one person in the family acting as a caregiver for the older adult with the qualifying ADL criteria and the caregiver has to leave the house to travel, the older adult would qualify for admission to the CIIC based on the available capacity of the facility on the appointment days.

These criteria can be revised by stakeholders depending on the estimates of the population to be served, budget of the municipality, and capacity of the facility.

Resources

To accommodate short-term stays, the CIIC intervention requires buildings and care facilities. Researchers have discussed this with the administrative officers of the study site subdistrict and obtained commitments to let the CIIC center use public buildings and infrastructure with beds, bathrooms, kitchens, washrooms, air conditioners, televisions, refrigerators, and outdoor facilities such as gardens, walkways, and sports facilities for the 24/7 care of 5-10 older adults.

The CIIC facility will employ dedicated full-time auxiliary nurses and other staff for this research. The CIIC service will not be delivered by existing primary health care nurses. Therefore, the busy routine of the primary health care facility will not affect the CIIC service or be disrupted. Access to health care in case of medical care needs of the participants will be secured by establishing a link between the CIIC and primary health care center before starting the study. In addition, for smooth linkage, the researcher will link to local health facilities that will be coordinated by the local municipal authority before starting the study.

The existing universal health coverage scheme covers health services 100% free of charge. The primary health care services are accessible by any Thai citizen. There is a referral system to the secondary district hospital, and an ambulance service is also available 24 hours a day.

Outcome Measurements

Validated instruments commonly used in aging and LTC research were carefully selected in order to objectively assess the impact of the CIIC intervention. Most of the instruments exist in the Thai language and have been validated in previous studies and programs in Thailand. In addition, the research team will conduct pilot testing of the instruments for the target population and ensure the reliability of all the instruments in the study setting and context.

Primary Outcome

The primary outcome is the burden of family caregivers measured at a 6-month follow-up appointment. The CBI [14,15] will be applied to measure the family caregiver's burden at baseline (month 0) and then again at month 6. CBI is an internationally well-validated measurement tool with a 24-item, 5-point Likert scale with the following 5 dimensions: time

dependence burden (5 items), developmental burden (5 items), physical burden (4 items), social burden (5 items), and emotional burden (5 items).

The total scores will be summed, with total scores >36 indicating a risk of "burning out" whereas total scores >24 are considered indicative of "a necessity to seek some form of respite care."

Secondary Outcomes

Secondary outcomes consist of biopsychosocial indicators including ADL, depression, and QOL of older people, which will be compared between intervention and control groups.

Functional ability will be assessed by applying the Barthel Index for ADL assessment [16], which measures the level of ability for 10 basic items (bowel movement, incontinence, grooming, toileting, feeding, transfer, mobility, dressing, stairs, bathing). Total possible scores range from 0 to 20, with lower scores indicating increased disability.

Depression will be screened by applying the Geriatric Depression Scale (GDS), which is internationally commonly used, validated, and regularly used in Thailand [17].

Health-related QOL will be measured with the EQ-5D-5L questionnaire [18] using the EQ visual analogue scale (EQ VAS) [18,19]. A validated Thai version of the instrument is already available and will be used after piloting. The EQ-5D-5L measures 5 dimensions with 5 levels: mobility, self-care, usual activities, pain/discomfort, and anxiety. The EQ VAS is a measure of overall self-rated health status with a vertical VAS where the end points are labeled "Best imaginable health state" and "Worst imaginable health state."

Cost for the intervention will be calculated in terms of intervention cost, family cost, and community cost. The details of the intervention cost will inform the estimated cost when expanding the area covered by the CIIC services.

The first possible outcome of the implementation of the CIIC intervention is promoting the capacity of the family caregivers through technical training, early detection of dependency problems, and respite care when the caregiver is overburdened in addition to linking families and primary health care services. The intervention components such as the (1) community respite home and (2) technical capacity building of the caregiver are directly targeting the reduction of caregiver burden.

Therefore, we set caregiver burden as the primary outcome of the study. ADL is also an important outcome of the component. Although we set these as the primary and secondary outcomes, respectively, in terms of the research methodology, they are both important outcomes of the study.

Selecting an outcome that is directly related to most of the intervention practically, we chose caregiver burden as the primary outcome. In a country with an FLTC system as its backbone, this outcome is more practical.

Sample Size

A sample of 4000 community-residing older adults will be recruited, with 2000 adults in each arm of the study (control and intervention), which our calculations show should suffice

for the power required by the study. Including 1500 participants in each arm should be ample to detect the effect size difference of 0.5 unit with an SD of 4 between the 2 arms. STATA version 11SE (Stata Corporation, College Station, TX) was utilized for sample and power estimations. The precision levels applied are a *P* value of .05 with a 95% confidence interval. The sample size is inflated (1) for a design effect of 1.2 for applying a cluster randomized design and (2) to compensate for potential nonresponses and drop-outs of up to 20% during recruitment and the study. After inflation, a total sample size of 4000 is estimated to be required for the study. Moreover, the sample size will be sufficient for the estimation of key parameters such as mean CBI, ADL, and health-related QOL indicators in the study population.

There will be 6 clusters in each arm. The cluster size is in the range of 300-350. Within each cluster, individual participants meeting eligibility criteria will be recruited consecutively. Informed consent will be requested from a representative of each cluster before randomization and from each older participant and a family caregiver after randomization.

Randomization

Sequence Generation

Cluster randomization will be used to prevent contamination between the intervention subdistrict and control subdistrict [20]. It is not possible to randomize the villages from different administrative areas or municipalities and directly assign them

to an intervention and control arm. Internal randomization will be practiced to randomly recruit 6 eligible clusters within the intervention arm municipality, which has 10-15 villages; likewise, the same will be done in the control arm [20].

Random Allocation

A random number will be generated to recruit villages randomly within each arm. A statistician blinded to the study will generate random numbers for each arm of the study. Control arm and intervention arm villages are geographically distant and administratively exclusive, yet they are in the same province and similar demographically, socially, and culturally to evaluate social interventions.

Blinding

Double blinding is not possible. Participants are blind to the allocation. Participants and research assistants performing the assessment cannot know the random allocation to a cluster before the study begins. Bias and contamination are controlled.

Implementation

The details of the intervention are described in the Methods section (Figure 2). The overall study period is 2 years, which will allow a net intervention period of 6 months, with the remainder of the time spent on preparation for the study such as establishing the facility, recruiting human resources for the service and research implementation, and assessment and evaluation before and after the intervention (Figure 3).

Figure 2. Activities and services in the intervention and control arms of the Community-Integrated Intermediary Care (CIIC) trial, Thailand.

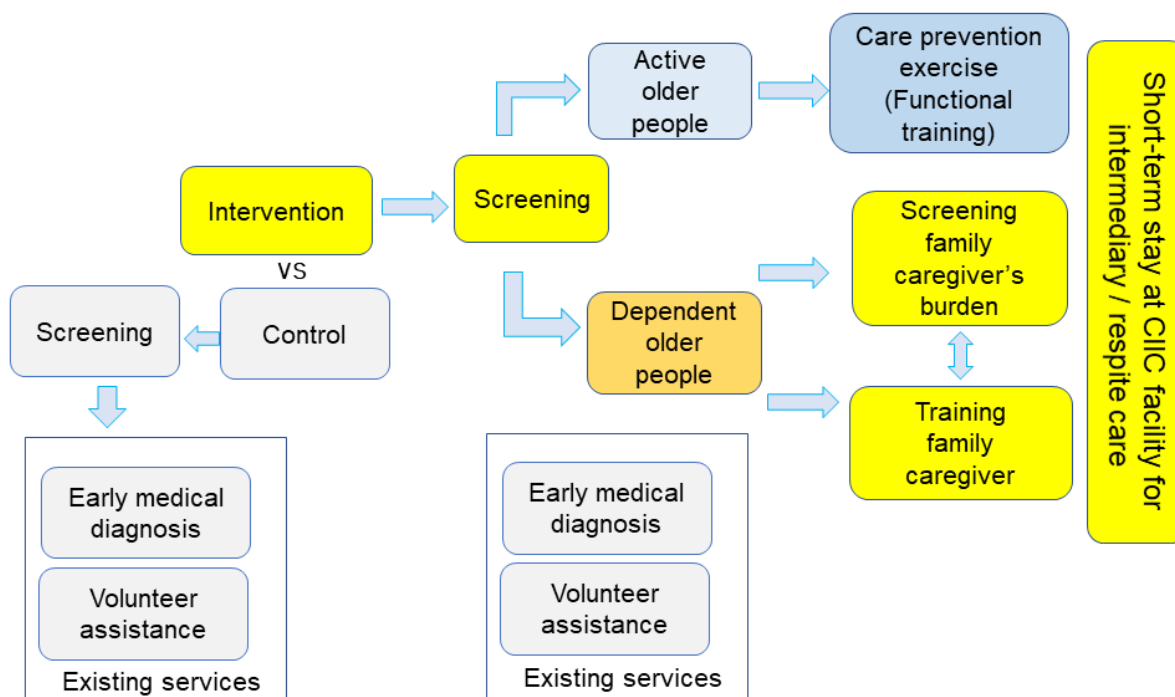


Figure 3. Timeline for the Community-Integrated Intermediary Care (CIIC) project, Thailand. C19: COVID-19 pandemic; P: PM 2.5 air pollution.

	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M13	M14	M15	M16	M17	M18	M19	M20	M21	M22	M23
	2019									2020									2021				
Activities for 2019-2021	May	June	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	June	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar
Identifying feasible clusters for the field experimental study and recruitment of the partner organizations such as municipalities, primary care centers, and hospitals	→	→	→																				
Preparing venues and facilities, supported by contributions from the local communities and authorities	→	→	→																				
CIIC auxiliary nurse selection, employment, and training	→	→	→																				
Screen all families with an elderly person in the intervention and control clusters (preassessment)																							
Baseline measurement of outcome indicators (preassessment) + data analysis					X	X	X	X	X														
Launching CIIC services + intervention								CIIC ready	CIIC ready	X					X	X	X	X	X	X			
Delay								P	P	C19	C19	C19	C19	C19									
Monitoring								X			X			X			X			X			
Postassessment																			X	X	X		
Data entry and data analysis																			X	X	X	X	X
Stakeholder meeting to prepare for sustainability							X			X									X				X
Final report, informing municipalities, and dissemination																			X	X	X	X	X

Data Collection and Follow-Up

Interviewer-administered, structured questionnaires will be used to collect the data. Follow-up will be comprised of (1) serial measurement of research outcomes, (2) monitoring the implementation for quality control, and (3) monitoring of serious adverse events related to the trial. Serial measurement of research outcomes will be applied, ensuring 6 months of follow-up for each participant. Baseline characteristics will be measured in both intervention and control arms before launching the CIIC service at the outset of the study. Postintervention, primary and secondary outcome measures will be measured again after 6 months of follow-up. There is minimal risk of drop-out from the study as the participants are long-term residents of the subdistricts.

Safety and Privacy Considerations

Confidentiality of data from the screening and intervention will be maintained by storing all paper-based patient material in locked cabinets accessible only to authorized personnel. Names or identity numbers of the patients will be excluded from the database. The databases are password protected and accessible only to authorized personnel and researchers. Participants will be informed that they are free to decide to leave the study without any impact on their privilege under the national health insurance.

Ethics and Trial Registration

The research project has been approved by the World Health Organization (WHO) Ethical Review Committee (WHO/ERC

ID; ERC.0003064) and Boromrajonani College of Nursing, Lampang Thailand Ethics Review Committee (E2562/005). It has been registered in the Thailand Clinical Trial Registry, with trial registration number TCTR20190412004.

Statistical Methods

The analysis will follow the intention-to-treat analysis approach. Outcomes will be compared between intervention and control clusters after 6 months of intervention.

To assess the effectiveness of the intervention, the primary outcome, CBI, will be compared between intervention and control arms after 6 months of intervention. Depending on the nature of the variables, *t* tests, chi-square tests of cluster summary measures, or multivariate analyses will be applied. Data distribution and homogeneity will be checked and ensure the assumption of statistical tests. Cluster-level summary statistics will be compared. A random effects model will be applied to control possible confounders in individual and cluster levels.

The intervention in the CIIC trial is a complex intervention with several components of prevention, training, and service. It is basically empowerment of the community. Therefore, a village as a random effect is due to population and social economic status, and participation of the community is considered as source of variation.

To evaluate the impact of the intervention on the secondary outcomes (ADL for dependency, GDS for depression, and

EQ-5D-5L for QOL), the analyses will compare the 2 arms by applying a multivariate analysis of variance model.

Afterwards, the cost of the intervention will be analyzed in terms of both the primary outcome and secondary outcomes. Statistical significance is defined as $P < .05$ with 95% confidence intervals.

Results

The CIIC facility has been established and equipped to provide care services to older persons who requested and were eligible to receive the service. Community-based care prevention programs have been launched in the intervention clusters. Nurses from the CIIC visited the houses of older persons upon the family caregiver's request for care planning advice. Family caregivers received training and assistance. However, the COVID-19 pandemic delayed the interventions (Figure 3).

Care prevention exercises have been launched in the communities of the 6 intervention clusters. The adoption rate was 100%. Community stakeholders, municipality authorities, and the Ministry of Public Health of Thailand actively collaborated with the research team. The community empowerment approach consisted of training volunteers to be trainers of the exercise groups, providing group exercise DVDs and televisions to use in the group exercise to each cluster, providing home exercise DVDs and posters for maintaining exercise at home, a calendar to record exercise frequency, and a line group for communication among the participants. Community-based, functional-training, group exercise activities were launched in February 2020. The research project provided DVDs free of charge to the intervention arm participants. During the suspension of the community-based activities due to the COVID-19 pandemic, care prevention exercises were sustained by applying home exercise.

The COVID-19 pandemic and declaration of emergency postponed the intervention program until June 2020. Afterward, the program was resumed. The study was implemented until December 2020. Since then, the CIIC trial is undergoing evaluation. The evaluation will be completed by the end of March 2021. The timeline for study implementation could be extended by the local ethical committee and WHO Ethical Review Committee.

Discussion

Principal Findings

Health and social care that is accessible in a universally covered scheme is an expectation of all second wave-aging countries like Thailand. They need an aging care model that can enhance FLTC and link to primary health care services, while being integrated into the community and local government in each municipality. CIIC is expected to provide a potential model that can link families and communities to local formal services and funding. In addition, it will promote active aging through a community-based care prevention exercise program for older persons.

The CIIC facility and services will introduce formal intermediary care services to the Thai community whereby informal care will be strengthened through helping families to improve their capacity for the care of older people [7]. Locating CIIC services in a neighborhood environment is designed to raise local attention and people's awareness, familiarity, and trust within the social network of the local community [21]. This is a strategy to realize the integration of older people into community care services.

Furthermore, we introduced 3 steps as part of a prevention strategy in the CIIC services (Figure 4). The first step is a community LTC prevention exercise program co-created to function as community empowerment. Participation in such community exercises can promote autonomy and active aging, with the potential outcome that will prevent dependency and need for LTC [22]. Second, when there is little care need, the older person can enjoy staying at home with their families, thereby improving their chances of "aging in place" [4]. When family caregivers face burnout, older persons will be able to access a formal care service in the community. Overall, families will be assisted through training, direct help, and a respite service provided by the CIIC [9]. Again, the hope is that it can prevent unnecessary LTC costs. Third, when older people remain active and healthy, health care needs may be reduced, thereby avoiding unnecessary hospital admission and saving health care costs. Screening of ADL and for common noncommunicable diseases will identify unmet needs earlier and prevent age-related morbidity and disability. Therefore, in the long-term, the interaction between the CIIC and primary health care services could be harmonized, leading to better integration and could be a step to realizing universal access to long-term and health care in Thailand.

Figure 4. Components of the intervention in the 2 arms of the Community-Integrated Intermediary Care (CIIC) trial.

	Intervention clusters	Control clusters
Timeline	Preparation Recruitment Screening Intervention Postevaluation	Preparation Recruitment Screening - Postevaluation
Recruitment	6 clusters	6 clusters
Screening	+	+
Care-prevention exercises in the community Intervention period of 6 months	+	
Enhancing family caregiver's capacity: on-demand training Intervention period of 6 months	+	
Community-integrated intermediary care for the older persons (Respite care) center Intervention period of 6 months	+	
Existing service: Primary health care service	+	+
Existing service: Volunteer-assisted care for bed-bound patients	+	+

Dissemination of Results and Publication Plan

A lay summary of the results will be communicated back to the communities via community radio and relevant social media outlets. The results will be reported back to the WHO Kobe Centre, published in international peer-reviewed journals, and relayed to the Ministry of Health of Thailand, local authorities, and development partners in aging and LTC services in the Asia-Pacific region.

Future Implications

With the CIIC model, the strategy for sustainability could be realized through mobilizing community participation and assets towards the shared value of active aging and sustainable social care for the older person. Therefore, we expect that the model of intermediary care in this study will yield a sustainable, affordable, and universally accessible model that could enhance FLTC in Thailand and other similar rapidly aging countries in Asia.

Challenges and Limitations

Cluster randomization may increase the risk of imbalance in the 2 arms at baseline. This approach of randomization we practiced in CIIC may have limitations but would minimize the residual confounders caused by differences in characteristics of the municipalities. However, this is the best pragmatic approach for the current trial. The results of randomization should be checked carefully at baseline by comparing the aggregate-level summary.

We do not have data about the desirability of temporary, short residential stays at the CIIC facility for older adults and their families. We may have underestimated the demand and therefore, also the required resources. Researchers have consulted with local governments about the possibility of tapping into reserve capacity and resources. Social distancing measures in the COVID-19 pandemic delayed the activities, but we adhered to those measures to ensure the safety of participants.

Conclusion

With a rapidly aging population, sustainable health and social care provided to older people in their community are urgently required. We see this as a potential step to the realization of

universal health coverage and well-established primary health care services that are inclusive of aging populations in Thailand. The evidence and lessons learnt in this study are expected to be beneficial to other similar countries in Asia.

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Conflicts of Interest

None declared.

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Abbreviations

ADL: activities of daily living
ASEAN: Association of Southeast Asian Nations
CBI: Caregiver Burden Inventory
CIIC: Community integrated intermediary care
EQ-5D-5L: EuroQol 5-dimensions 5-levels
FLTC: family-based, long-term care
GDS: Geriatric Depression Scale
LTC: long-term care
QOL: quality of life
VAS: visual analogue scale
WHO: World Health Organization

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Protocol

A Pharmacist and Health Coach–Delivered Mobile Health Intervention for Type 2 Diabetes: Protocol for a Randomized Controlled Crossover Study

Lisa Kay Sharp¹, BSc, MA, PhD; Alana Biggers², MD, MPH; Rosanne Perez², BSc; Julia Henkins², BA, MPH; Jessica Tilton³, PharmD; Ben S Gerber², BSc, MPH, MD

¹Department of Pharmacy Systems, Outcomes & Policy, College of Pharmacy, University of Illinois at Chicago, Chicago, IL, United States

²Department of Medicine, Section of Academic Internal Medicine & Geriatrics, University of Illinois at Chicago, Chicago, IL, United States

³Department of Pharmacy Practice, College of Pharmacy, University of Illinois at Chicago, Chicago, IL, United States

Corresponding Author:

Lisa Kay Sharp, BSc, MA, PhD

Department of Pharmacy Systems, Outcomes & Policy, College of Pharmacy

University of Illinois at Chicago

833 S Wood St

Chicago, IL, 60611

United States

Phone: 1 3123553569

Email: sharp1@uic.edu

Abstract

Background: Aggressive management of blood glucose, blood pressure, and cholesterol through medication and lifestyle adherence is necessary to minimize the adverse health outcomes of type 2 diabetes. However, numerous psychosocial and environmental barriers to adherence prevent low-income, urban, and ethnic minority populations from achieving their management goals, resulting in diabetes complications. Health coaches working with clinical pharmacists represent a promising strategy for addressing common diabetes management barriers. Mobile health (mHealth) tools may further enhance their ability to support vulnerable minority populations in diabetes management.

Objective: The aim of this study is to evaluate the impact of an mHealth clinical pharmacist and health coach–delivered intervention on hemoglobin A_{1c} (HbA_{1c}, primary outcome), blood pressure, and low-density lipoprotein (secondary outcomes) in African-Americans and Latinos with poorly controlled type 2 diabetes.

Methods: A 2-year, randomized controlled crossover study will evaluate the effectiveness of an mHealth diabetes intervention delivered by a health coach and clinical pharmacist team compared with usual care. All patients will receive 1 year of team intervention, including lifestyle and medication support delivered in the home with videoconferencing and text messages. All patients will also receive 1 year of usual care without team intervention and no home visits. The order of the conditions received will be randomized. Our recruitment goal is 220 urban African-American or Latino adults with uncontrolled type 2 diabetes (HbA_{1c} ≥8%) receiving care from a largely minority-serving, urban academic medical center. The intervention includes the following: health coaches supporting patients through home visits, phone calls, and text messaging and clinical pharmacists supporting patients through videoconferences facilitated by health coaches. Data collection includes physiologic (HbA_{1c}, blood pressure, weight, and lipid profile) and survey measures (medication adherence, diabetes-related behaviors, and quality of life). Data collection during the second year of study will determine the maintenance of any physiological improvement among participants receiving the intervention during the first year.

Results: Participant enrollment began in March 2017. We have recruited 221 patients. Intervention delivery and data collection will continue until November 2021. The results are expected to be published by May 2022.

Conclusions: This is among the first trials to incorporate health coaches, clinical pharmacists, and mHealth technologies to increase access to diabetes support among urban African-Americans and Latinos to achieve therapeutic goals.

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KEYWORDS

mHealth; type 2 diabetes mellitus; community health workers; clinical pharmacists

Introduction

Background

Diabetes disproportionately affects African-American and Latino adults in the United States compared with Whites [1]. Not only is the prevalence of type 2 diabetes approximately 1.5 times greater, but diabetes-related outcomes are consistently worse. Aggressive management of blood glucose, blood pressure, and cholesterol through medication and lifestyle adherence is necessary to minimize adverse health outcomes [2,3]. However, fewer than 20% of African-Americans and Latinos reach all therapeutic goals [4-11]. Adherence to medication is generally poor [12]: 20%-30% of prescriptions are never filled (due to cost or concerns of side effects), and 50% of medications for chronic disease are not taken as prescribed [13-15]. Additional barriers to physical activity [16] and healthy eating [17] behaviors are common within urban neighborhoods where low-income African-Americans and Latinos reside. Access to healthy foods and safe areas for physical activity are often limited. As a result, adherence to the recommended diet and physical activity is low for a majority of minorities with type 2 diabetes [18,19]. Additional barriers to self-management among low-income, minority populations include low health literacy, depression, lack of social support, poor patient-clinician communication, limited access to health care, and language (particularly Latinos who prefer Spanish for communication with providers) [20-27].

Four large systematic reviews of intervention studies aimed at improving medication adherence have concluded that few existing interventions improved clinical outcomes beyond adherence alone [13,14,28,29]. In addition, the reviews highlighted concerns regarding the abundance of studies with small sample sizes and the underrepresentation of ethnic minorities, especially Latinos. Components of the most effective interventions often included behavioral strategies and incorporated pharmacists [30]. Pharmacist-led interventions enhance adherence to chronic disease medication and health behaviors through patient education, use of adherence aids, and addressing medication-related issues (eg, drug interactions and cost) [14,31-36]. Clinical pharmacists have expertise in medication management and the ability to adjust therapy in collaboration with providers [37-42]. Within the United States, most state boards of pharmacy authorize collaborative drug therapy management protocols between clinical pharmacists and prescribers [42-45].

More recently, 2 pragmatic studies of chronic disease management employed multifaceted interventions delivered by clinical pharmacists using telephone-based brief negotiated interviewing, a variant of motivational interviewing [46,47]. First, Choudhry et al [46] studied patients within a large multispecialty medical group including 488 patients with diabetes and others with hypertension or hyperlipidemia that were poorly controlled. A statistically significant improvement in medication adherence failed to translate into any significant

improvement in clinical outcomes for patients with diabetes or the other chronic conditions. In the second study, Lauffenburger et al [47] enrolled members of the largest health insurer in New Jersey with similar results. However, in a secondary analysis of 196 participants with diabetes who completed at least one telephone pharmacy consultation, hemoglobin A_{1c} (HbA_{1c}) decreased (difference between intervention and propensity score matched comparison group: mean decrease in HbA_{1c}-0.48 with a 95% CI of -0.91, -0.05). Although both studies included ethnic minorities, subgroup analyses to explore the impact of the intervention based on ethnicity were not reported.

Health coaches (HCs) may extend the ability of clinical pharmacists to support medication adherence in low-income minority populations. HCs alone have been shown to contribute to improvements in diabetes self-management and HbA_{1c} levels [48-55]. Trained HCs are trusted by patients, understand sociocultural barriers, and can help increase the relevancy of disease self-management to individuals who manage competing priorities. Our previous research demonstrated that HCs can successfully collaborate with clinical pharmacists in addressing lifestyle and medication adherence [56], with unclear evidence of improved clinical outcomes [15]. In our initial efficacy trial of African-American and Latino patients with uncontrolled type 2 diabetes, we demonstrated a modest reduction in HbA_{1c} with pharmacist support alone (mean decrease in HbA_{1c} -0.45%; with a 95% CI -0.96, 0.05), which was similar to the change observed with HC-augmented pharmacist support (mean decrease in HbA_{1c} -0.42% with a 95% CI -0.93, 0.08). However, many participants did not fully engage with the pharmacists, which required transportation to the clinic for in-person visits. Importantly, 80.4% (152/189) of our study sample surveyed expressed interest in participating in a mobile health (mHealth) approach with pharmacists and HCs.

To address patients' feedback and enhance our clinical pharmacist and HC support, we designed this study, which incorporates mHealth (text messaging and videoconferencing) combined with in-person HC support. Videoconferencing in diabetes care is practical, potentially cost-effective, and reliable for disease management [46,57,58]. Despite the heterogeneity found in studies conducted in various countries with diverse patient populations, telemedicine interventions produce significantly better glycemic outcomes than usual care [59]. Videoconferencing with clinical pharmacists to promote medication adherence is a growing model in practice but is not well studied, particularly with mobile devices or involving urban, low-income minority patients [60,61]. Our inclusion of HCs to assist pharmacists in the delivery of videoconferencing services is further aimed at supporting adherence efforts and improving outcomes. In addition, HCs use text messaging to provide social support and improve self-efficacy and adherence. Text messaging interventions in diabetes management have shown encouraging results, targeting both medication adherence and lifestyle modification with a reduction in HbA_{1c} [60-64]. Although no specific text messaging components have been

linked to improved outcomes, follow-up contact, individualized frequency, and tailored content are likely important components [65,66].

Drawing upon the need to develop new models of care that address the needs of those most adversely impacted by diabetes, our team has developed an innovative clinical pharmacist and HC mHealth model to improve HbA_{1c} (primary outcome). This model targets African-Americans and Latinos (both English- and Spanish-speaking) with uncontrolled diabetes [20,56]. This paper describes our currently implemented mHealth study protocol and includes a crossover randomized controlled trial.

Objectives

The aim of this study is to evaluate the impact of an mHealth clinical pharmacist and HC intervention in African-Americans

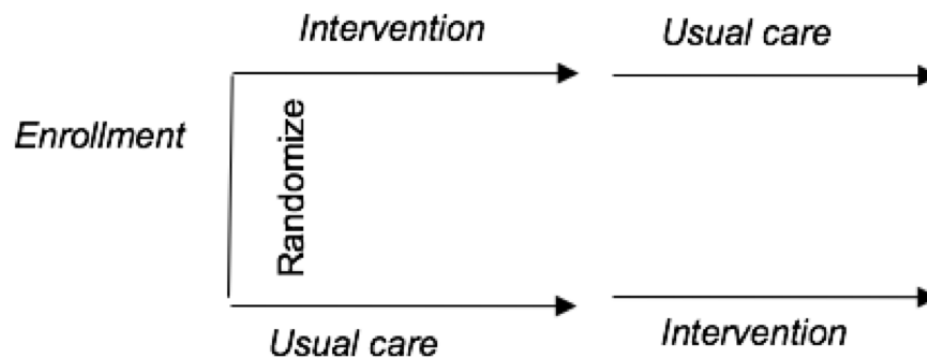
and Latinos with poorly controlled type 2 diabetes. We hypothesize that the mHealth intervention will improve HbA_{1c}, blood pressure, and low-density lipoprotein (LDL) as well as medication and lifestyle behavior adherence compared with usual care. In addition, the crossover design will test the hypothesis that improvements in outcomes resulting from the intervention in year 1 will be maintained during the maintenance period (usual care) in year 2.

Methods

Study Design

As shown in Figure 1, a randomized controlled crossover study will evaluate the effectiveness of an mHealth intervention delivered by a clinical pharmacist and HC versus a usual care group.

Figure 1. Randomized crossover study design.



The primary outcome is the change in HbA_{1c} level. Secondary outcomes include changes in blood pressure and LDL cholesterol levels. Using a 1:1 ratio, we will randomize 220 patients to either (1) a mHealth intervention delivered by a clinical pharmacist and HC for 1 year, followed by usual care for 1 year, or (2) usual care for 1 year, followed by the mHealth intervention for 1 year. Both groups will crossover at the end of year 1, such that those receiving the mHealth intervention during the first year will receive usual care during the second year (to evaluate potential maintenance of outcome improvement). Similarly, those with usual care in year 1 will crossover to receive the intervention in year 2 (to ensure that all subjects are able to receive the intervention). Of note, we do not consider HbA_{1c} levels collected at the end of year 1 when crossover occurs. The treatment received by patients (intervention or usual care) will change at the end of year 1, independent of HbA_{1c} levels.

Separate randomization schedules generated in REDCap will be used for each of the 4 main clinical sites with stratification for ethnic group (African-American and Latino) and gender to balance the proportion of participants across randomized conditions. All study procedures have been approved by the University of Illinois at Chicago Institutional Review Board (IRB 2016-0380).

Setting and Recruitment

The study will be conducted at the University of Illinois Hospital and Health Sciences System (UI Health), which includes both inpatient and outpatient facilities serving an urban, largely minority population in Chicago. All outpatient sites share access to the electronic medical record (EMR), Cerner Powerchart.

An initial pool of potential patient participants will be identified through EMR queries and include all patients registered in 4 UI Health internal medicine or family practice clinics. Patients with a documented diagnosis of type 2 diabetes and HbA_{1c} ≥ 8 in the last year will be targeted for recruitment. The study team will mail study introductory letters by post to those patients identified from the EMR queries meeting the two initial criteria. The letter explains that if the patient is not interested in being contacted by telephone regarding the study, they should either mail back the enclosed prepaid card or call the telephone number provided to indicate that they are not interested in being contacted further (*opt-out*). Individuals who do not *opt out* are called by a research assistant (RA) to determine study interest and assess eligibility. Eligible and interested patients are scheduled to complete written consent, Health Information Portability and Accountability Act (HIPAA) authorizations, and baseline data collection with a data collector at the Clinical Research Center at UI Health. Additional recruitment is completed by RAs present within the clinics who receive referrals directly from the staff. A study physician reviews patients' EMR to confirm eligibility (Textbox 1).

Textbox 1. Inclusion and exclusion criteria.**Inclusion criteria:**

- Self-identified as Latino or Hispanic or African-American
- Verbal fluency in English or Spanish
- Latest hemoglobin A_{1c} $\geq 8.0\%$ (within 6 months)
- History of type 2 diabetes (>1 year)
- Aged between 21 and 75 years
- Mobile phone or text messaging plan
- Agrees to home visits by health coach
- Receives primary care at clinical site (>1 year)

Exclusion criteria:

- Unable to verbalize comprehension of study or impaired decision making (eg, dementia)
- Lives outside Chicago (≥ 3 months/year)
- Household member already participating in same study
- Plans to move from the Chicago area within the next year
- Pregnant or trying to get pregnant
- Unable to send or read text message on mobile phone
- History or planned gastric bypass or transplant surgery

mHealth Intervention**Clinical Pharmacist**

During the intervention year, patients receive pharmacist videoconferences facilitated by an HC who is in the patient's home with a tablet (iPad with cellular plan). The initial pharmacist encounter is scheduled after the HC has already conducted 1-2 home visits and lasts 60 minutes. The pharmacist initially reconciles medications via videoconferencing with HC assistance. Subsequent pharmacist encounters vary in frequency based on patient needs and range in length from 30 to 60 minutes. HCs schedule videoconference appointments during dedicated days or times when pharmacists are available. Videoconferences are conducted using VSee software. VSee transmits personal health information securely and is available for use on desktop computers and mobile devices providing real-time person-to-person audio and video communications. However, it is most suitable for health-related communication, as it is Food and Drug Administration registered and HIPAA compliant (using FIPS 140-2 certified 256-bit Advanced Encryption Standard). Finally, it uses *peer-to-peer* sessions so that information is not stored on a server.

Pharmacist services are based on a standardized pharmacist management protocol. After the initial medication reconciliation, follow-up pharmacist activities include reviewing home glucose and/or blood pressure, monitoring log data obtained by the HC during home visits, identifying therapeutic goals for HbA_{1c} and blood pressure collaboratively with patients' primary care providers (PCPs), formulating an approved plan of care, assessing changes in medications, and documenting the plan in the EMR. In addition, pharmacists provide education related to medication (name and purpose of medications and time,

strength, and method of administration); drug interactions and side effects; goals of therapy; basic lifestyle modifications; and use of pillboxes, low-literacy visual medication lists, or other adherence aids. Pharmacists educate and encourage lifestyle changes, consistent with the published guidelines [67-69]. They propose medication changes based on algorithms and protocols derived from national guidelines under physician guidance [70-72]. Pharmacists routinely monitor hypoglycemic events, address prevention, and review treatments. This includes 3 steps: (1) addressing hypoglycemia with every patient contact, (2) applying principles of appropriate therapy (education, empowerment, frequent glucose self-monitoring, flexible medication regimen, individualized goals, and professional guidance), and (3) considering risk factors for hypoglycemia. Overall, there is mixed evidence regarding the benefits of aggressive glycemic control [73-75]. In the proposed study, PCPs and pharmacists adopt the American Diabetes Association approach to individualized care, where the general goal for nonpregnant adults is HbA_{1c} less than 7%. They may decide upon less stringent goals for those with a history of severe hypoglycemia, limited life expectancy, advanced complications, or extensive comorbid conditions [76]. In addition, pharmacists follow the 2018 American College of Cardiology or American Heart Association guidelines for lipid management (eg, calculating 10 year atherosclerotic cardiovascular risk to determine statin intensity) [77].

EMR Documentation and PCP Communication

PCPs and pharmacists communicate routinely regarding patient care and are located in the same area within the medical setting. Pharmacists review EMRs, including blood test results, clinical progress notes, problem and medication lists, drug allergies, hospitalization records, and emergency room reports. Nonurgent

communication and electronic progress notes from each pharmacist encounter will be sent to the PCP through inbox messaging and note forwarding within the EMR. Pharmacist progress notes include a detailed list of medications, estimated adherence levels, and home glucose or blood pressure monitoring log information.

Videoconference Training

Videoconferencing procedures in the intervention follow the American Telemedicine Association practice guidelines [68]: (1) pharmacist and patient/HC identity verification, (2) informed consent, (3) appropriate physical environment (privacy, lighting, and noise), (4) education and training (pharmacist and HC), (5) alternate communication (eg, telephone contact in case of disruption of service), and (6) documentation in UI Health EMR (by pharmacist and HC). All study pharmacists and HCs receive standardized training on the use of videoconferencing, which includes scheduling, preparing the environment (home or pharmacist office), patient education on telehealth, and documentation. All encounters have contingency plans in place for technology problems (eg, inadequate signal for video streaming through iPads), including the use of mobile phones for all HCs.

HC

HCs will introduce themselves to the patients in person at the data collection visit that aligns with the beginning of the patients' intervention year (ie, baseline visit or crossover visit at the beginning of year 2 depending on randomization). When possible, the first home visit will be scheduled at the initial introductory meeting. If this is not possible, the HC will follow up by telephone within 1 week to schedule the first home visit. All HCs are either African-American or bilingual or bicultural Latino and work with patients who are concordant for race or ethnicity and language. The HCs have an undergraduate college degree in or related to community health with experience conducting home visits. Specific training for the research study includes 80 hours of standardized HC training or retraining. As outlined in [Textbox 2](#), training begins with an overview of the research protocol and discussion of the HC goals. The

fundamental components of providing health support to marginalized populations are addressed with the required reading materials, didactic presentations, and discussions [78].

HC training highlights the unique qualification of HCs to provide culturally sensitive support, tailor visits based on the personal preferences of participants, and assist patients in navigating the health care system [79,80]. Diabetes education follows the Diabetes Education Empowerment Program, which targets literacy and cultural awareness [81], and the Training Curriculum for Health Coaches [52,82]. Training includes shadowing a clinical pharmacist to understand medication use, adherence, glucose and blood pressure monitoring, insulin injection, and medication reconciliation. The study investigators provide training in videoconferencing (eg, scheduling and practice encounters), text messaging (eg, practice with the custom text messaging platform and standardized safety procedures), and conducting home visits in a culturally sensitive manner. Ongoing training is provided periodically on topics that reinforce and expand the initial training (eg, motivational interviewing and insulin management). HCs receive routine orientation to clinical operations and staff at their primary care locations. Standardized safety procedures related to text messaging and home visits are also addressed. To evaluate clinical skills, the HCs demonstrate reliable measurement of blood sugar, blood pressure, and administration of insulin (though HCs do not administer insulin to patients).

The HC component involves monthly home visits with ongoing telephone support, including the facilitation of all pharmacist videoconferences. The HCs work with the pharmacist to evaluate adherence (eg, check label instructions and fill and expiration dates of pill bottles), assist in medication reconciliation, review home glucose and/or blood pressure monitoring data, and provide reinforcement of proper medication use. Finally, HCs debrief patients after pharmacist encounters to reinforce and clarify recommendations and plans. HCs and pharmacists communicate with each other between videoconference encounters by phone or secure email, as needed, to coordinate efforts.

Textbox 2. Summary of health coach training.

Introduction to research study

- Project history and overview
- Study protocol
- Institutional Review Board and human subjects research training

Role of health coaches (HCs)

- Core competencies and roles of HCs
- Role of HCs in addressing health disparities
- Understanding trauma and supporting survivors

Navigating the health care system

- Primary care clinic workflow
- Navigating electronic medical record and encounter documentation
- Patient advocacy and empowerment
- “Closing the loop,” connecting patients to care

Diabetes education

- Understanding diabetes and risk factors
- Disease pathophysiology, complications

Disease management

- Blood glucose monitoring
- Medication therapies for diabetes
- Medication reconciliation, adherence
- Treating hypoglycemic events
- Nutrition and physical activity education

Health coaching strategies

- Patient-centered collaboration
- Motivational interviewing
- Specific, measurable, achievable, relevant, and time-specific goals
- Stress reduction, coping with depression

Home visits and safety

- Ethical considerations, boundary setting
- Cultural humanity
- Safety guidelines and self-defense

Mobile health technology

- Videoconferencing software (VSee)
- MyTapp text messaging system
- Best practices for telehealth encounters

Home visits include the HC and patient. Family members are permitted by patient requests. Through open discussion and reflective listening, HCs encourage patients to explore their emotions and share their concerns [83]. Overall, HCs provide diabetes self-management education and support (DSME/S), consistent with the recommendations of the American Diabetes

Association’s position statement [83]. Specifically, HCs provide DSME/S that includes the following over the course of the 1-year intervention: engagement, information sharing, psychosocial and behavioral support, integration with other therapies, and coordination of care. Initial HC encounters focus on relationship building and gaining an understanding of the

patient's individualized diabetes education needs. HCs provide diabetes education and consider realistic and achievable food choices, portion sizes, and cooking preparation; discuss relationships between medications, meals, and glucose levels; and help patients integrate movement into their daily lifestyles. Diabetes education is facilitated by our culturally appropriate multimedia education eBook, *Living Well with Diabetes/Viviendo Bien con Diabetes* [84]. This eBook (available in English and Spanish) provides patients with video testimonials and various interactive educational experiences. HCs present specific chapters on an iPad to reinforce specific diabetes self-management concepts [84]. To promote behavioral change, HCs use motivational interviewing techniques to assist patients in setting specific health behavior change goals. Goals set jointly by HCs and patients follow the specific, measurable, achievable, relevant, and time-specific (SMART) framework [85]. Providing social support while helping patients engage with their existing support systems offers the potential of long-term behavior change beyond the duration of the research period. Educating patients on how to effectively navigate the health care system and use existing resources promotes continued self-efficacy. In summary, HC interactions are culturally tailored to individual needs, preferences, and resources to provide DSME/S [86].

By the end of the second month, HCs will facilitate a videoconference encounter with a pharmacist and patient to conduct a complete medication reconciliation. HCs work with patients to identify adherence barriers and assist in problem solving or referrals for resources aimed at overcoming

recognized challenges in medication use. Finally, HCs document summaries of each encounter (with or without videoconferencing) in the EMR and forward notes electronically to PCPs and pharmacists.

Text Messaging

Between home visits, HCs will communicate with patients through telephone calls and text messaging. All text messages will be tailored by HCs and sent through a custom software app (*mytapp*). We developed *mytapp* for community-based health behavior research. *mytapp* sends messages immediately or at a scheduled date or time, recurrent messages (daily, weekly, or weekdays), group messages, or multiple question surveys. HCs receive training on *mytapp* and schedule messages for their patients regarding appointments and medications. HCs send messages to maintain motivation, elicit feedback on progress, and screen for barriers that may reduce the chance of success (Table 1). For example, a morning text message may ask a patient how they did on their goal the previous day.

No more than 7 messages are delivered weekly, except for optional medication reminders. For safety, patients are reminded that text messages are sent in an automated fashion by a computer. Furthermore, they are reminded that urgent health questions should be directed to their PCP and not sent in a text message. HCs monitor patient responses through their study phones.

Texts are monitored by the HCs with additional oversight by the project coordinator.

Table 1. Example text message templates.

Message type	Example
Medication reminder	"Hi, Ms. Brown, just checking to see if you took your morning pills."
Refill reminder	"Make sure you don't run out. Check to see when a pill refill is due."
Appointment reminder	"Just a reminder that you have a doc's appointment today."
Goal monitoring	"Remember your goal. Did you take your meds last night?"
Glucose monitoring	"Hello, Mr. Marquez, have you had time to check your sugar today?"
Self-efficacy	"Taking your meds is within your control. You can do it."
Motivation	"You have come a long way! Keep up the good work!"

Usual Care

All participants spend 1 year in the usual care condition, either year 1 or 2, depending on the randomization. During receipt of usual care, they receive health care from their usual providers without the support of a pharmacist or HC. There are no home visits or pharmacist telehealth videoconferencing encounters with usual care. In addition, participants receive a 1-page list of clinic resources with names and direct telephone numbers (eg, social worker or clinical pharmacist) along with a low-literacy, paper-based diabetes education pamphlet [87]. Usual care reflects the type of health care that patients receive outside of any participation in research.

Intervention Fidelity

To continuously evaluate the fidelity of both conditions, we review logs maintained by the HCs weekly, including visit dates,

length of visits, visit content, and disposition (eg, visit completed, and patient unreachable). Weekly group meetings with HCs and the research team provide an opportunity to monitor intervention delivery. Monthly lunch meetings with clinical pharmacists, HCs, and investigators ensure active collaboration between HCs and pharmacists. All technology-related difficulties are reported to the coordinator immediately and discussed in weekly meetings with the investigators. One investigator, a health psychologist, maintains weekly contact with HCs to provide emotional support and incorporate structured training opportunities. Text messages sent and received via *mytapp* are reviewed monthly.

Data Collection

Trained, blinded RAs collect physiological and self-report data through interview administration within the clinical research center at UI Health at 5 time points: baseline and every 6 months

for 2 years. RAs are matched to patient language preferences in English or Spanish. Laminated cards with Likert-type scale responses are provided as a visual reference to the patients. Interview data are entered directly into laptop computers using Research Electronic Data Capture (Vanderbilt University) electronic data capture web application [88]. The baseline survey requires an average duration of 60 minutes with subsequent follow-up visits lasting 30 minutes. Subjects receive US \$30 as compensation for travel and time at each of the 5 data collection points (plus US \$50 if at least one videoconference is completed in the prior 6 months during the intervention period). Public transit cards and parking passes are provided when needed. Participants are informed of their randomization assignment at the end of the baseline data collection.

Sociodemographics include age, gender, self-reported race and ethnicity, country of origin, income, highest level of education, employment status, global health status [89], and insurance. Diabetes and medical history include self-reported time since diabetes diagnosis, prior receipt of diabetes education, current therapy, known diabetes complications, and comorbid conditions. Health literacy is assessed using 3 screening questions with high discriminatory power among English- and Spanish-speaking populations [67,90,91]. Mobile phone use and comfort sending text messages is also assessed using 5 items [68].

Intermediate variables are also collected at each of the 5 time points. Perceived severity of diabetes and perceived susceptibility are assessed using 2 items adapted from the study by Bradley et al [92]. The perceived benefits of therapy are measured by a 5-item survey related to the benefits of therapy [71]. Diabetes distress is measured using the brief Diabetes Distress Scale [73]. Depression is measured using the Patient Health Questionnaire [75,76]. Social support is measured using an assessment of the amount of total support received and satisfaction with support from family, friends, and the health care team [93]. Self-efficacy is measured using the Stanford 8-item self-efficacy for diabetes survey [94]. Contextual data include an environmental survey that addresses loneliness, social cohesion, and neighborhood safety as well as the identification of stressful life events [95-97].

HCs record the dates of patient contacts in REDCap (eg, phone calls and home encounters). Clinical progress notes are completed in the EMR after every participant contact (by phone if longer than 15 minutes and in-person). Information includes mode, time, location (home vs clinic), content of contact, results of glucose or blood pressure self-monitoring, goals, life events, pharmacist interactions, and interventions. Intensification of therapy will be defined as the number of dosage increases of antihypertensive, hypoglycemic agent, or insulin or the addition of a new agent since the baseline visit [98-100]. Chart review will define the number of PCP visits and pharmacist videoconferences as well as the number of pharmacist- or physician-initiated medication changes.

Physiologic outcomes will be collected at 5 time points (0, 6, 12, 18, and 24 months). The research staff will perform phlebotomy, blood pressure, weight, and height recordings. HbA_{1c} and fasting lipid profile (total cholesterol, high-density

lipoprotein, LDL, and triglycerides) are obtained via phlebotomy. A calibrated digital scale measures weight. A height stadiometer measures height, with subjects removing their shoes (for BMI assessment). Blood pressure is assessed in subjects sitting down for at least 5 minutes, following a standard procedure. Health-related quality of life is measured using the EuroQol Group 5D and Diabetes Distress Scale [73].

The revised Summary of Diabetes Self-Care Activities Measure captures basic diet, exercise, blood sugar testing, foot care, and smoking with 11 core items [101]. Additional questions address skipping medications and insulin injections to evaluate adherence, as well as taking aspirin regularly. Alcohol misuse is assessed using the Alcohol Use Disorder Identification Test—Concise [102].

Sample Size Justification

The sample size calculation is powered to detect the primary outcome, which is the change in HbA_{1c}. Reviews of published studies suggest that successful education programs lower A_{1c} levels by 0.4% to 1.7% [3,103]. On the basis of our previous experience with the patient population, we estimated a mean baseline HbA_{1c} level of 10% with a SD of 1.8 and an effect size of 0.56 for aim 1. The cross-time correlation was estimated to be 0.30, with a compound symmetry structure. We adjusted for clustering and assumed an intraclass correlation coefficient of 0.01, with 5 clusters. This yielded a design effect of 1.34. Two-sided alpha of .05 and 80% power were assumed. Allowing for a 20% dropout rate, 220 patients were required [104].

Data Management and Analysis

To address missing data, we will examine the data for patterns of missingness and potential bias in missingness. If data are not missing at random, we will apply one of several available imputation methods in a sensitivity analysis based on the nature and extent of missing data [105]. We will determine effectiveness using intention-to-treat principles with actual imputation of missing data [106-109]. This will allow us to appreciate the potential biases inherent in a *real-world* setting due to dropout and poor adherence to study procedures.

Patients who share a single PCP might exhibit similarities that are not shared with patients cared for by other PCPs. To address this, we will include random effects in the model for clinic site, PCP, and HC (though the small numbers of HCs may call for a fixed effect approach or *insufficient replication*) [110]. To examine a stricter examination of effect, we will also do a *per-protocol* analysis of complete cases. Completed cases will not be dependent on intermediate time point data collections (6 and 18 months). Potential selection bias will be corrected by including model covariates that are differentially related to study participation.

Univariate comparisons between the 2 study groups for outcomes and covariates at baseline will be conducted using chi-square tests for categorical variables, Kruskal-Wallis tests for ordinal variables, and *t* tests for continuous variables. All tests will be two-sided. Nonnormal continuous data will be transformed before the analysis. To provide a comprehensive analysis of our primary hypothesis, we will extend the usual

analysis of crossover designs [111] by including a longitudinal trend component in the first year. Thus, we can examine the time course (0, 6, and 12 months) as linear or quadratic over the first 3 measurements. This will allow us to investigate whether changes are made early and at what rate they continue throughout the rest of the period. This analysis permits a comparison of the trends between the 2 conditions. In addition, we will regard subjects as a random effect and will use Gaussian mixed model estimation. We can then substitute treatment by period interactions for the carry-over effects, and the model can be reduced in a recommended sequence (first omit carry-over, then omit treatment, and finally omit period) [111]. We will also explore patterned covariance structures such as compound symmetry and autoregression along with incorporating time-constant and time-varying covariates, such as health literacy or diabetes distress.

The primary analysis of all physiological outcomes jointly in the repeated measures design will be conducted using a general linear model framework. Repeated measures multivariate analysis of variance will be used to explore the simultaneous impact of the treatment on multiple correlated dependent variables, including the use of Roy-Bargmann stepdown F tests and discriminant function analysis as post hoc tests to identify subsets of outcome measures affected [112]. Multivariate analysis of variance (MANOVA) secondary analyses will explore the impact of inhomogeneous baseline variables on the results. Group by time-trend interaction contrasts will be used to explore different group trajectories of change. The potential consequences of medication intensification (eg, initiation of insulin) will be explored by evaluating changes in BMI and quality of life.

Exploratory subgroup analyses will follow a heterogeneity in treatment effects framework [113,114]. We will determine which subjects in the intervention group had the greatest improvement in outcomes, based on multiple prespecified patient characteristics, including race (African-American or Latino), depression, comorbidities, baseline behaviors, health literacy, continuity of care, and social support. These analyses will also consider additional comparisons between subjects above and below the median levels of videoconferencing and text

messaging activity. Statistical tests will be implemented as interactions within the full data set.

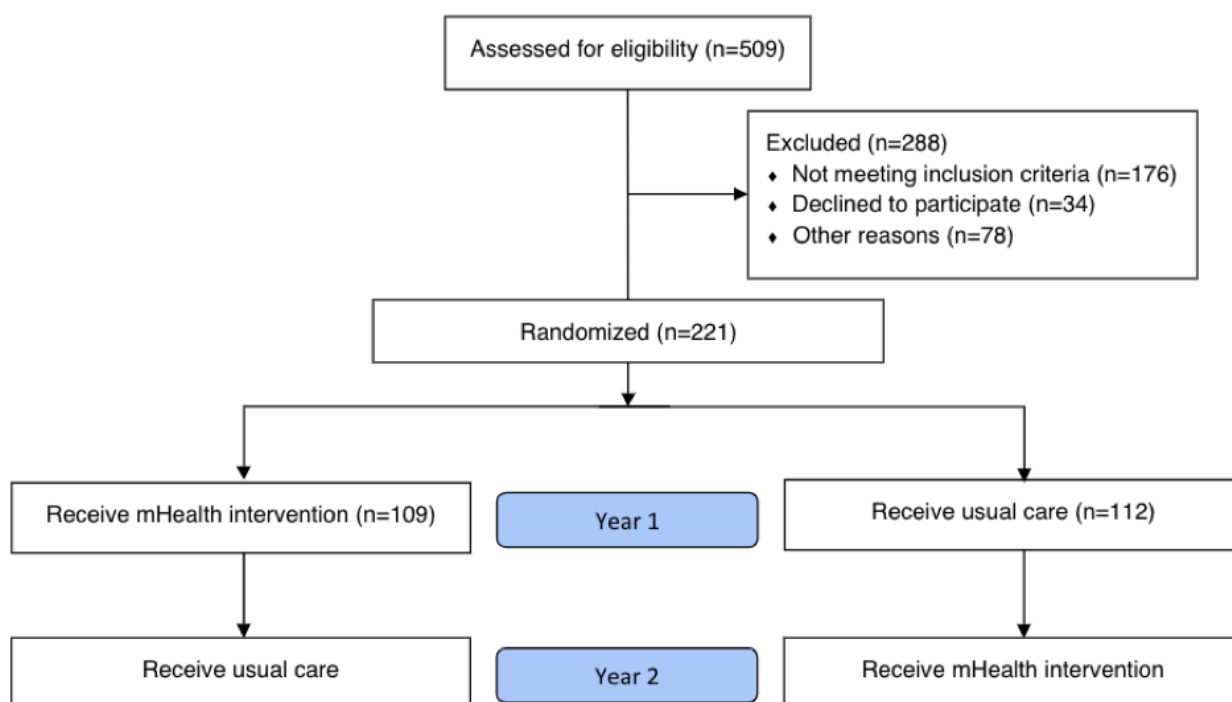
If the intervention results in improved HbA_{1c} more than that in the usual care, we will examine whether changes in self-efficacy, health beliefs, or social support serve as mediators for improved outcomes. In addition, we will explore diabetes-related behaviors as well as medication treatment intensification as mediators using MPlus [115-118]. To further identify the relative contributions of videoconferencing and/or text messaging, we will conduct mediational modeling with videoconferencing time, number of text messages, and HC contact time as mediating variables. This may describe any dose-response relationship between mHealth utilization and outcomes. We will compute bias-corrected bootstrap standard errors using MPlus. This offers accurate confidence intervals for mediation coefficients [119]. Due to anticipated relationships between HC activity level and mHealth delivery, we plan to inspect correlations between mediators and incorporate any significant findings in model development. This analysis will demonstrate whether the intervention effects are sensitive to mediators. Finally, given the sample size, observed (rather than latent) variables will be used in the mediation models. To enhance the power of mediation modeling, we adopt an $\alpha=.10$ type I error criterion to improve the chances of finding promising mediators for future studies.

We expect a limited amount of decline in physiologic outcomes with the transition back to usual care. We will test the hypothesis that improvements in HbA_{1c} (primary outcome), blood pressure, and LDL cholesterol (secondary outcomes) will be maintained during the maintenance period. The analyses will be conducted in a manner similar to our primary hypothesis and will evaluate changes in the initial intervention group 1 year after intervention completion.

Results

The study was initiated in July 2016, and enrollment began in March 2017. Figure 2 shows the Consolidated Standards of Reporting Trials diagram for recruitment.

Figure 2. Consolidated Standards of Reporting Trials flow diagram. mHealth: mobile health.



As shown in [Table 2](#), 221 patients have been enrolled, exceeding our goal of 220 patients. A total of 112 patients have been randomized to usual care for their first year, and 109 patients have been randomized to the mHealth intervention.

The retention rate is currently 90% for subjects completing the first year of the study. We anticipate that data collection will be completed in November 2021. Following data analyses, the manuscript will be developed with primary results by May 2022 for peer-reviewed publication.

Table 2. Demographic characteristics of study population.

Characteristic	Usual care (n=112)	Intervention (n=109)
Age (years), mean (SD)	54.5 (9.6)	56.0 (9.3)
Diabetes duration (years), mean (SD)	12.3 (7.9)	13.1 (7.7)
Ethnicity, n (%)		
Latino or Hispanic	36 (32.1)	37 (33.9)
African-American	76 (67.9)	72 (66.1)
Gender, n (%)		
Male	35 (31.2)	32 (29.4)
Female	77 (68.7)	77 (70.6)
Language preference, n (%)		
English	97 (86.6)	87 (79.8)
Spanish	15 (13.4)	22 (20.2)
Income (US \$), n (%)		
Less than 10,000	38 (33.9)	36 (33.0)
10,000-19,999	19 (17.0)	26 (23.8)
20,000-29,999	12 (10.7)	16 (14.7)
30,000-39,999	7 (6.2)	10 (9.2)
40,000-49,999	12 (10.7)	0 (0)
50,000-59,999	6 (5.4)	8 (7.3)
60,000-69,999	2 (1.8)	3 (2.8)
70,000 or more	14 (12.5)	8 (7.3)
Refused to answer	2 (1.8)	2 (1.8)
Education, n (%)		
Less than high school	26 (23.6)	29 (26.6)
High school diploma or equivalent	22 (19.6)	33 (30.3)
Some college, 2-year certificate, or associates degree	41 (36.6)	26 (23.8)
College graduate (4 year)	11 (9.8)	13 (11.9)
Some graduate school	3 (2.7)	3 (2.8)
Graduate degree	8 (7.1)	5 (4.6)
Other	1 (0.9)	0 (0)
Health status, n (%)		
Excellent	2 (1.8)	0 (0)
Very good	4 (3.6)	5 (4.6)
Good	42 (37.5)	38 (34.9)
Fair	47 (42.0)	58 (53.2)
Poor	17 (15.2)	8 (7.3)
Insurance, n (%)		
None	5 (4.5)	8 (7.3)
Public	69 (61.6)	70 (64.2)
Private	36 (32.1)	30 (27.5)
Other	2 (1.8)	1 (0.9)

Discussion

This study assesses the effectiveness of a novel mHealth approach for improving diabetes self-management in an underserved, minority population with type 2 diabetes. The study will provide further evidence of the use of mHealth in both clinical and community environments, with tools to support clinical pharmacists and HCs in their patient-oriented activities. If effective, this intervention can be considered for implementation in low-resource settings where pharmacist services are not readily available, and HCs can extend the reach of providers targeting patients with limited access to care.

Strengths and Limitations

The study is innovative in several ways. The proposed study will be the first randomized controlled trial to evaluate an mHealth intervention to improve diabetes management in low-income African-Americans and Latinos with type 2 diabetes delivered through HCs. This study builds upon prior work and is responsive to patient feedback in offering remotely delivered videoconferencing with clinical pharmacists who collaborate with HCs to improve diabetes outcomes [56]. Pharmacist videoconferencing overcomes the transportation barriers commonly experienced by individuals with limited income. We currently use scalable, inexpensive mHealth tools (VSee and

mytapp) to promote adoption in low-resource clinical organizations, including Federally Qualified Health Centers.

A number of limitations and challenges have been identified. First, there is the potential for contamination across groups, as randomization was not clustered. Intervention and usual care patients may share the same provider and clinical site. In addition, we recruited patients from a single urban health care system, which may limit generalizability. Additional studies in practice networks would require the availability of clinical pharmacists and HCs. Finally, our intervention integrates multiple components: clinical pharmacists, HCs, videoconferencing, and text messaging, so we are unable to determine the impact of each component individually.

In conclusion, despite the widespread use of mobile devices, little is known about the effectiveness of the technology in improving health care delivery or outcomes. Although systematic reviews show the preliminary value of text messaging, patient education apps, and videoconferencing in chronic disease management, most studies have been small in size, underpowered, and low in quality and include motivated, nonminority subjects. This study will provide the evidence needed on the impact of mHealth diabetes adherence support delivered to low-income minority patients with uncontrolled type 2 diabetes.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-review report by National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

[PDF File (Adobe PDF File), 167 KB - [resprot_v10i3e17170_app1.pdf](#)]

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Abbreviations

DSME/S: diabetes self-management education and support

EMR: electronic medical record

HbA1c: hemoglobin A1c

HC: health coach

HIPAA: Health Information Portability and Accountability Act

LDL: low-density lipoprotein

MANOVA: multivariate analysis of variance

mHealth: mobile health

PCP: primary care provider

RA: research assistant

UI Health: University of Illinois Hospital and Health Sciences System

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Protocol

The Impact of a Web-Based Mindfulness, Nutrition, and Physical Activity Platform on the Health Status of First-Year University Students: Protocol for a Randomized Controlled Trial

Claire F Trottier¹, BSc; Jessica R L Lieffers², PhD, RD; Steven T Johnson³, PhD; João F Mota⁴, PhD; Roshni K Gill¹; Carla M Prado¹, RD, PhD

¹Human Nutrition Research Unit, Department of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, AB, Canada

²College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, SK, Canada

³Faculty of Health Disciplines, Athabasca University, Athabasca, AB, Canada

⁴Clinical and Sports Nutrition Research Laboratory (LABINCE), Faculty of Nutrition, Federal University of Goiás, Goiânia, Brazil

Corresponding Author:

Carla M Prado, RD, PhD

Human Nutrition Research Unit

Department of Agricultural, Food and Nutritional Science

University of Alberta

2-004 Li Ka Shing Centre for Health and Innovation

8602 - 112 Street

Edmonton, AB, T6G 2R3

Canada

Phone: 1 780 492 7934

Email: cprado@ualberta.ca

Abstract

Background: First-year university students are at an increased risk for developing mental health issues and a poor nutritional status. Self-care plays an essential role in optimizing mental health and can prevent or manage stress, anxiety, and depression. Web-based self-monitoring of diet and physical activity can lead to similar or improved health outcomes compared with conventional methods. Such tools are also popular among university students.

Objective: The primary aim of this 12-week randomized controlled trial is to assess the impact of a web-based wellness platform on perceived stress among first-year university students. The secondary aim is to assess the effects of the platform on diet quality. The exploratory objectives are to explore the effects of the platform on body composition, health-related quality of life, mindfulness, mental well-being, and physical activity.

Methods: A total of 97 first-year undergraduate students were randomized to either the intervention (n=48) or control (n=49) group. The intervention consisted of access to a web-based platform called My Viva Plan (MVP), which aims to support healthy living by focusing on the topics of mindfulness, nutrition, and physical activity. The platform is fully automated and guided by the principles of cognitive behavioral theory. Participants in the intervention group were instructed to use the MVP as frequently as possible over 12 weeks. The control group did not receive access to MVP. Perceived stress was assessed using the Stress Indicators Questionnaire at baseline, week 6, and week 12. Three-day food records were used to analyze the dietary intake at baseline and week 12. Health-related quality of life, mindfulness, mental well-being, and physical activity questionnaires were completed at baseline, week 6, and week 12. Body composition was assessed at baseline and week 12. Study assessments were completed in person at baseline and week 12 and electronically at week 6.

Results: Study recruitment started in August 2018, with batch enrollment for students registered in the fall (September 2018 to December 2018) and winter (January 2019 to April 2019) academic terms at the University of Alberta, Edmonton, Alberta.

Conclusions: This study is the first to explore the impact of a web-based platform designed to promote health and wellness on perceived stress and diet quality among first-year university students.

Trial Registration: ClinicalTrials.gov NCT03579264; <https://clinicaltrials.gov/ct2/show/NCT03579264>.

International Registered Report Identifier (IRRID): DERR1-10.2196/24534

KEYWORDS

internet-based intervention; wellness programs; dietary intake; physical activity; mindfulness; quality of life; randomized controlled trial

Introduction

Background

University students are at risk of developing mental [1] and physical [2-4] health problems. The number of students reporting symptoms of anxiety [5], depression [5], and suicidal thoughts [1,6] continues to rise, and this is a greater concern among first-year undergraduate students [7]. During this important yet vulnerable period of their lives, students not only transition from adolescence to adulthood but also start to face challenging situations and the new responsibilities of career development and a self-sufficient life [8]. This specific period and situation is related to neurobiological, behavioral, and environmental changes that impose significant psychological stress [9,10] and an increase in the risk of psychiatric disorders [11].

In addition to mental health, during the first year of a university program, students' dietary habits and physical activity are also negatively impacted [2,3,12,13]. Students increase their consumption of unhealthy, energy-dense foods and reduce their intake of healthy, nutrient-dense foods in their first year of university, resulting in an overall decrease in diet quality [13]. These changes may result in unfavorable alterations of their nutritional status, such as an increase in body weight and fat mass [3,13,14]. In a meta-analysis of 5549 university students, the mean weight change during the first year was 1.36 kg (95% CI 1.15-1.57 kg) [15]. Hoffman et al [3] observed an increase of 0.7% of fat mass among first-year university students, which further illustrates the physical changes that are observed in this population.

Increased psychological stress and poor nutritional status can hinder students' quality of life [16], hinder academic performance [17], and increase morbidity [18] and mortality [19]. Apart from the direct impact on students, mental health problems in the general population and workforce impose a significant financial burden on the health care system [20,21]. Universities may be the last setting in which mental health programs can be promoted to a large portion of young adults before they enter the diversified workforce [22]. Therefore, the development of programs focused on the mental and physical health status of university students is of special interest.

University students rely heavily on technology to perform tasks of daily living, and health care is no exception [23]. The use of electronic tools to monitor health status is increasing in the general population. Of the expected 80-100 billion smart devices in the world by 2020, approximately 26 billion will be used to monitor aspects of personal health and well-being [23]. Therefore, individualized technological tools encompassing aspects of practicality, availability, cost, and time efficiency are promising health promotion approaches for this generation (ie, generation Z).

Research has shown that electronic monitoring of diet or diet and physical activity can lead to similar or better health outcomes compared with conventional methods such as paper-based food records and weight loss resulting from counseling with practitioners [24-27]. Although digital health apps for nutrition, physical activity, and mental health are extremely popular among young adults [28], many of these tools have not been designed by health care professionals [29,30] and lack a sound evidence base [31]. Moreover, previous research has shown that poor integration between nutrition and physical activity apps or trackers is a concern among users [32].

Considering the limitations of many available eHealth tools, My Viva Plan (MVP; [Multimedia Appendix 1](#)) [33] addresses some common shortfalls as it was developed by a registered dietitian (Loreen Wales, Revive Wellness Inc) in collaboration with other health care professionals (registered psychologists, certified personal trainers, and kinesiologists). It focuses on multiple pillars of health: mindfulness, nutrition, and physical activity. MVP is a publicly accessible web-based program available via paid subscription. The platform can be used as a stand-alone intervention or in combination with coaching from professionals. MVP has 3 variations of the platform to target different populations: 1 variation targeted at the general population and 2 variations targeted at students attending local postsecondary institutions. The variation used and described in this study is the variation that is targeted at students attending the University of Alberta (Edmonton, Alberta).

Objectives and Hypothesis

The main objective of this 12-week randomized controlled trial is to assess the impact of MVP on perceived stress among first-year university students. The secondary objective is to assess the impact on diet quality, and exploratory objectives will assess the impact on body composition, health-related quality of life, mindfulness, mental well-being, and physical activity. It was hypothesized that using an integrated web-based wellness platform that encompasses the 3 pillars of preventative self-care (mindfulness, nutrition, and physical activity) would help guide health behavior, resulting in improved perceived stress and diet quality in first-year university students.

Methods

Study Design and Ethical Considerations

This 2-armed, parallel, randomized controlled trial was conducted at the Human Nutrition Research Unit (HNRU), University of Alberta, and used an embedded mixed methods design [34,35]. The research protocol is approved by the University of Alberta Ethics Board (Pro00079680) and complies with the standards set out in the Canadian Tri-Council Policy statement on the use of human participants in research. Before the commencement of the study, all participants were informed in person of the procedures and potential risks involved in the

investigation and were asked to provide written informed consent. All participants, regardless of group assignment, received CAD \$50 (US \$39) cash and one year of free membership to MVP after completing all study assessments.

Research Participants

First-year undergraduate students at the University of Alberta were recruited using a variety of techniques (in-class invitations, in person through flyers distributed at special events and locations, email, social media, and advertisements placed on notice boards on campus) during the fall (September 2018 to December 2018) and winter (January 2019 to April 2019) terms. Various campus faculties were targeted for recruitment to ensure a diverse sample. Eligible participants were males and females aged 17-30 years who were able to complete all study assessments in their first year of undergraduate studies. Reasons for exclusion included any self-reported eating disorder; self-reported untreated depression, anxiety, or mood disorder; pregnancy or lactation; not having a device to access the internet (ie, computer, smartphone, tablet); not able to communicate in English; or having an electronic implantable device (because of body composition assessment). Participants were assumed to have strong computer and internet literacy, given the typical age and education level of the study population; however, literacy levels of the participants were not assessed.

Screening, Randomization, and Treatment Allocation

Potential participants contacted the research team and underwent prescreening using the same method in which they contacted the research team (ie, via email or over phone). The research team discussed the responsibilities of the participants (ie, time commitment of each study visit and a commitment of 12 weeks of participation) and addressed any questions before scheduling the baseline visit. The screening criteria were later confirmed and documented in person at the baseline visit. A member of the research team reviewed the study consent form in detail with each participant during their baseline visit, and participants received a copy of their signed study consent form for their records. All eligible and consenting participants were randomly

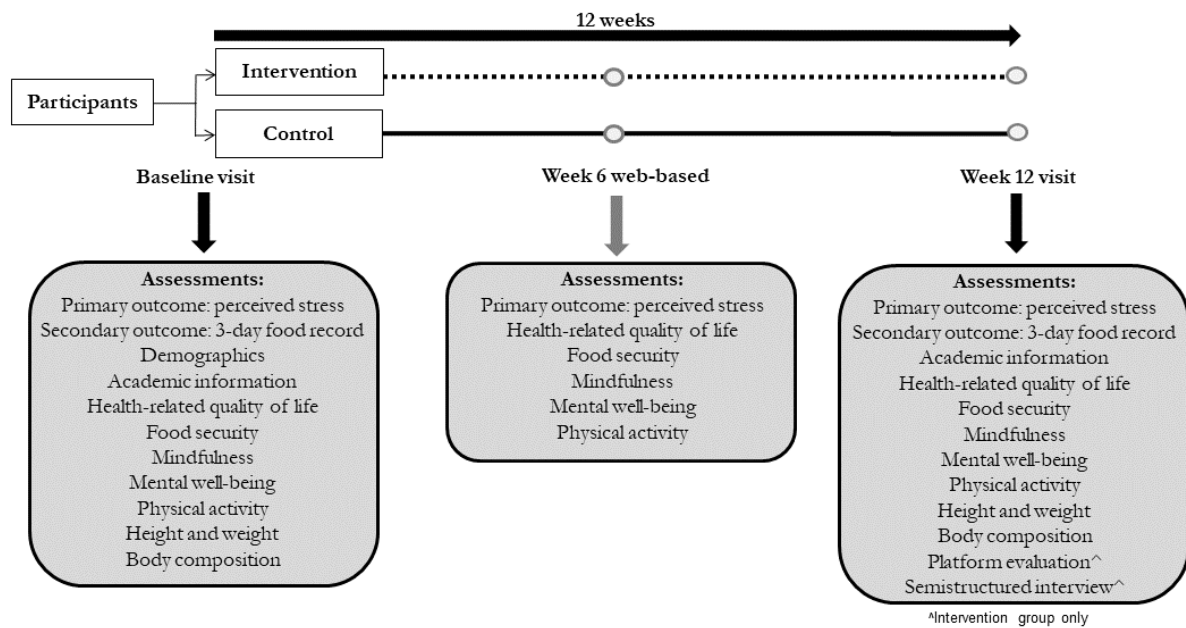
assigned by block randomization to the intervention (platform use) or control (no intervention) group in a 1:1 allocation ratio. Blocks were stratified by sex to balance sex distribution and block sizes randomly alternated between blocks of 2 and 4 to minimize the risk of predictable group allocation [36].

The allocation sequence was generated by an independent biostatistician and uploaded onto Research Electronic Data Capture (REDCap) [37,38], where it was concealed from the study team. The study team enrolled and assigned the participants to the groups using REDCap. The participants and researchers were not blinded to the group assignment because of the nature of the study. The staff needed to know the participants' group assignment to provide access to the platform, monitor use, and schedule interviews.

Experimental Protocol

Participants allocated to the intervention group were instructed to use MVP as frequently as possible for the duration of the 12-week period. Participants allocated to the control group were asked to maintain their usual lifestyle throughout the study and did not receive access to MVP during the 12 weeks of study participation. In-person study visits occurred at baseline and week 12 at the HNRRU (Figure 1), and the following assessments were collected: academic information, anthropometry, body composition, demographics (at baseline only), dietary intake, food security, health-related quality of life, mindfulness, mental well-being, perceived stress, and physical activity (Multimedia Appendix 2). At week 6, questionnaires were electronically administered (Figure 1) and collected via web-based surveys through REDCap [37,38] to assess food security, health-related quality of life, mindfulness, mental well-being, perceived stress, and physical activity (Multimedia Appendix 2). Participants assigned to the intervention group were asked to evaluate MVP by questionnaire at their week 12 visit and participate in a one-on-one semistructured interview to gather qualitative information on their experiences with and perceptions of MVP. Details of the qualitative analysis are published in a separate publication.

Figure 1. Outline of the experimental protocol.



Intervention

The principles of cognitive behavioral theory (CBT) [39], specifically the social cognitive theory of self-regulation [40], were used to guide the development of the MVP platform. The goal is to build resilience and self-efficacy through the development of strong self-care habits. The platform included features such as goal setting, diet plans, exercise tutorials, and self-monitoring of health behaviors (ie, stress levels). The variation of the platform used in our study was fully automated, with no human interaction. The University of Alberta logo is displayed on the log-in page of MVP and on any exercise video made in collaboration with the University of Alberta's Campus and Community Recreation facilities; however, institutional logos were not present anywhere else within the platform.

All participants in the intervention group received free access to the same version of the MVP, and membership access was delivered by email within 5 days of completing baseline assessments. While using the platform, users were prompted to create a profile and fill in the basic medical history questions, including food allergies, medical conditions, and current medications. A video tutorial provided guidance on the platform and recommended that new users start with the mindfulness component. The tutorial explained that each component of the platform can be used independently or in combination and that users could set up a shortcut on their mobile device to directly access the MVP platform. No additional MVP training was provided by the researchers.

The 3 core components of MVP are described as follows:

1. My Mind encourages goal setting, daily reflections, and quarterly stress assessments. One of the first steps in setting up an MVP account is the goal-setting process. The platform allows users to set a maximum of 3 short-term and 3 long-term goals. Participants set their own goals, which could be modified at any time. The platform also advises users to keep their goals specific, measurable, achievable,
2. My Nutrition contains meal plans, recipes, grocery shopping list, cooking demonstrations, Vivapedia (an encyclopedia on the nutritional benefits of numerous food items and nutrients), and a guide with suggested menu items from restaurants and fast-food chains in Edmonton and on the University of Alberta's campus. Meal plans allow users to create their own plans for meals each day or to have a plan built for them. When a user builds their own meal plan, the number of suggested portions of protein, grains, fruits, vegetables, dairy, and fat are generated by the platform to fit the recommendations of the Eating Well with Canada's Food Guide [41], and the user can choose foods from each food group, either from a drop-down list or by manually entering the food item, to reach these targets. Menu plans built by the platform for the user are based on the user's preferences and meet the recommendations of the 2007 Eating Well with Canada's Food Guide [41]. Platform-derived meal plans can be customized for allergies, intolerances, and other food preferences (ie, vegetarian, gluten-free, nut-free, dairy-free) and provide brief instructions on how to prepare each meal. A serving size guide is available within the platform and as a printable handout. The recommended proportion of foods from each food category is represented as a dinner plate model for users to refer.
3. My Fitness provides a physical activity scheduler and video tutorials for workouts and yoga. The workout tutorials have

realistic, and time-oriented. Examples of goals include "I will stretch every night before bed" (short term) and "I will train for a marathon this year" (long term). Daily reflections on stress levels, eating habits, physical activity, and steps taken toward achieving goals are encouraged. On the basis of the responses from the daily reflections, the user's progress is viewable in a graphical format (such as a bar graph to indicate the level of stress on each day of the week and a checkmark on days of the week that steps were taken to achieve goals).

accommodations for self-described fitness level, equipment availability, and desired duration, whereas the yoga tutorials incorporate guided meditations and can be adjusted by self-described fitness level and desired duration. Video workouts included resistance training, aerobic exercises, and stretching. In addition, users can log the duration and intensity of their workouts completed outside the platform.

To help foster learning in a wide range of individuals, the platform provides educational resources in multiple formats, including video content and printable handouts. MVP employs strategies commonly used in clinical practice, such as CBT, into daily reflections of health behaviors. Outside of the platform, coaching tips that provide messages of healthy living (ie, being present, seeking accountability, healthy snacking, keeping active) are emailed on a weekly basis and presented in the same sequence for all users. Users also receive student-specific messages in key times throughout the academic year (ie, managing the first week of a new academic term, preparing for midterm exams, preparing for final exams). The content of these email messages is not tailored based on the user's activity within the platform.

Assessment of Study Outcomes

Primary Outcome

Our primary outcome is the difference in change over time in perceived stress (baseline to week 12) between the groups. Perceived stress was measured using the self-reported Stress Indicator Questionnaire [42]. Total scores range from 73 to 365 points, with higher total scores indicating higher levels of perceived stress.

Secondary Outcome

Our secondary outcome is the difference in the change of diet quality between the groups. Dietary intake was assessed using paper-based 3-day food records that were analyzed using Food Processor Nutrition Analysis Software, version 11.0.3 (ESHA Research). Participants were asked to enter information about all the food, beverages, and supplements they consumed over 3 days, with 2 of the days on a weekday and 1 of the days on a weekend day. Instructions on how to complete the food records were included at the beginning of the paper food record booklet. In addition, instructions on how to complete food records were provided in person with participants during their baseline visit.

Diet quality was estimated using the nutrient rich food (NRF) index version 9.3 [43,44]. This index calculates a nutrient density score based on the amount of nutrients per 100 kcal serving of an individual food item: saturated fat, sodium, total sugar, protein, fiber, iron, magnesium, calcium, potassium, and vitamins A, C, and D. The percent daily value was calculated for all the nutrients. The sum of the percent daily values of nutrients to limit (saturated fat, sodium, and total sugar) was subtracted from the sum of nutrients to encourage (protein, fiber, iron, magnesium, calcium, potassium, and vitamins A, C, and D) to obtain the NRF score for that food item.

Vitamin D was chosen to replace vitamin E because it has been identified as an important nutrient for encouraging [45,46]. For protein, the lower limit of 10% of calories from protein in a

2000-kcal diet was used based on the acceptable macronutrient distribution ranges [47]. The percent daily values used in this study were 20 g saturated fat, 2400 mg sodium, 100 g total sugar, 50 g protein, 25 g fiber, 14 mg iron, 420 mg magnesium, 1100 mg calcium, 4700 mg potassium, 1000 retinol equivalent vitamin A, 60 mg vitamin C, and 600 international unit vitamin D.

To limit the effect of fortified foods, percent daily values were capped at 100%. A low or negative NRF score indicates a low-nutrient-dense food, and a high or positive NRF score indicates greater nutrient density. The total score was calculated by averaging all individual food scores within a 3-day food record.

Exploratory Outcomes

The following exploratory outcomes were assessed and will be compared within groups (over time) and between groups at the end of the 12-week intervention period:

- Body composition was assessed by a hand-to-foot multifrequency bioelectrical impedance analysis using the QuadScan 4000 (BodyStat). Participants were instructed to fast for 5 hours before testing (drinking water only) and to avoid intense physical activity for 12 hours. Immediately before testing, participants were instructed to remove their shoes, socks, and all metal accessories before lying in a supine position. Fat mass, fat-free mass, and total body water were estimated based on device-specific equations.
- Health-related quality of life was assessed using the self-administered 12-Item Short-Form Health Survey version 2 [48]. Physical and mental component summary scores on a scale of 0 to 100 were generated and interpreted against data from the general population of the United States. Higher scores indicate a greater quality of life [49], and a difference in summary scores between 3 and 5 points is considered clinically significant [50].
- Mindfulness was assessed using the self-administered Five Facet Mindfulness Questionnaire (FFMQ) [51]. The FFMQ contains 39 statements about 5 facets of mindfulness (observation, description, awareness actions, nonjudgment, and nonreactivity) that are rated and scored on a 5-point Likert-type scale from never true to always true. Construct validity of the FFMQ has been demonstrated [52].
- Mental well-being was measured using the self-administered Warwick-Edinburgh Mental Wellbeing Scale [53]. The 14 questions on aspects of mental well-being were assessed using a 5-point Likert scale that was used to score each question and summed for a total score, with a higher score indicating higher mental well-being [53].
- Physical activity was assessed using a validated, self-administered Godin-Shephard Leisure-Time Physical Activity Questionnaire [54]. The number of times in a typical week that strenuous, moderate, and mild or light activity longer than 15 minutes during free time was reported. A score was calculated based on the number of times per week multiplied by an intensity factor (9 for strenuous, 5 for moderate, and 3 for mild or light). On the basis of the total score, the amount of activity was classified as active, moderately active, or sedentary [55].

Other Assessments

Demographic information collected included sex, age, ethnicity, and current type of residence. Self-reported academic information collected included the degree type and the number of enrolled courses. Academic performance was evaluated based on students' self-reported grades. Trained staff measured the participant's anthropometrics and instructed participants to wear light clothing and remove their footwear. The body weight was measured using a calibrated digital scale (Health o meter Professional Remote Display, Sunbeam Products Inc) to the nearest 0.1 kg. Height was measured using a 235 Heightronic Digital Stadiometer (Quick Medical) to the nearest 0.1 cm. BMI was calculated and evaluated using previously defined categories [56]. Food security was assessed using a 6-question survey, as described by Entz et al [57].

Participants in the intervention group were asked to evaluate MVP at the week 12 visit using the Mobile App Rating Scale questionnaire [58]. Subscales for the following sections were calculated: engagement, functionality, esthetics, and information quality. To account for possible ratings of *not applicable*, the mean is calculated for each subscale and summed to generate a mean total score, where a higher total mean score represents a positive evaluation.

Intervention Preference and Website Usage Data

System-obtained data were collected directly from the MVP for participants allocated to the intervention group. These data included information on the total number of log-ins, duration of activity, and usage of specific components of the app (ie, frequency of daily reflections, frequency of planned physical activities). A member of the study team reviewed participants' platform usage every 3 weeks to assess the log-in activity. Individuals who had been identified as not logging on to the platform in that 3-week period were contacted by a member of the research team via email or over phone to ask if their ability to access the platform had been impeded and to act as a reminder of their agreement to use the platform as frequently as possible.

Data Management

Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Alberta [37,38]. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to

common statistical packages, and (4) procedures for data integration and interoperability with external sources. Data collected using paper files at baseline and week 12 were transferred into REDCap and reviewed by an independent researcher within the team to identify data entry errors. At week 6, the study questionnaires were delivered electronically through REDCap and collected directly from the participant. Platform-obtained data were managed using Microsoft Excel (Microsoft Corporation).

Statistical Analysis and Power and Sample Size Rationale

Statistical Analysis

Our analysis of the primary outcome will be based on an intention-to-treat analysis using inverse probability weighting. Our analysis of the secondary and exploratory outcomes will be based on per-protocol and intention-to-treat analyses using inverse probability weighting. The effects of intervention over time will also be investigated using a generalized estimating equation. SPSS 25 (IBM Corporation) statistical software will be used for the data analysis. Characteristic variables will be compared between the 2 treatment groups and between those that did and did not complete the study. Differential variables will be used as covariates in the statistical analyses. $P < .05$ will be considered statistically significant.

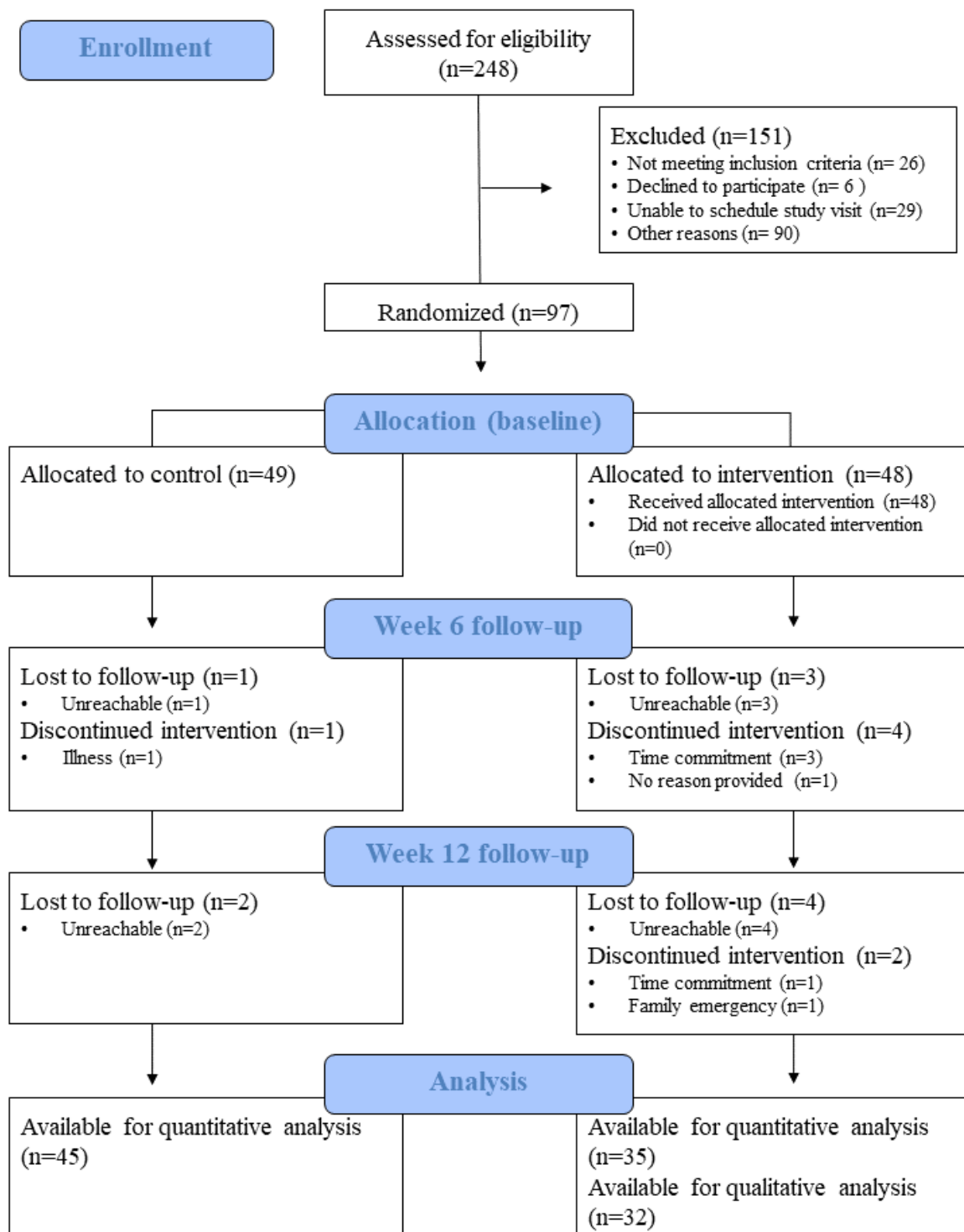
Power and Sample Size

The sample size was calculated using G-Power software (version 3.1.9.2, Heinrich-Heine-Universität Düsseldorf) [59] and based on the perceived stress scale scores of distressed adults after an internet-based stress management intervention [60]. With effect sizes of 0.74, a level of significance of 5%, and statistical power of 95% ($\text{power} = 1 - \beta = 0.95$), the number of participants required is 33. With an anticipated attrition rate of 20%, we aimed to recruit 100 participants and have 80 participants complete the intervention.

Results

Study recruitment began in August 2018. Batch recruitment was used for enrollment in the fall (September 2018 to December 2018) and winter (January 2019 to April 2019) terms, with 37 and 43 participants completing the study in the fall and winter terms, respectively. A total of 80 participants completed the 12-week trial ($n = 35$ in the intervention group; $n = 45$ in the control group; Figure 2).

Figure 2. Flow diagram.



Discussion

Strengths

This study used a mixed methods design to capture both quantitative and qualitative findings from first-year university students' experiences using MVP and is comprehensive in the variety of data captured. The MVP platform itself has a different approach than other web-based tools as it focuses on multiple

pillars of health (mindfulness, nutrition, and physical activity), provides a comprehensive list of resources to its users, is developed by certified health professionals, and is guided by principles of CBT. In addition, the issues commonly experienced by university students were strongly considered in the development of MVP. For example, MVP delivered messages about stress management during key times in the academic term and guides to healthy eating on campus, further supporting healthy food choices.

Limitations

Potential limitations of the study are related to the inclusion of only first-year university students and the monitoring of platform usage, which may have limited external validity. Attrition was higher in the group that received the intervention than in the control group, although platform usage data have not yet been analyzed. This suggests that systematic differences between groups should be examined in outcome analyses. Finally, all limitations will be examined and taken into account in the interpretation of the results.

Conclusions

Preventative self-care is important for first-year university students who may not have established this skill and are simultaneously experiencing new stress and pressures of postsecondary education. Targets were obtained for the sample size. This study will determine whether the web-based platform has a direct impact on health and wellness among first-year university students and could become an important tool for virtual, preventative self-care delivery.

Acknowledgments

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Conflicts of Interest

Revive Wellness Inc has no role in the design of the study, data collection analysis and interpretation, or the writing and decision for publication of the manuscript. RG is an undergraduate student who is a part-time nutrition coordinator at Revive Wellness. Her participation in this paper was unrelated to this work, as she volunteered for this research project.

Multimedia Appendix 1

Screenshots of My Viva Plan.

[PDF File (Adobe PDF File), 3394 KB - [resprot_v10i3e24534_app1.pdf](#)]

Multimedia Appendix 2

Study timeline.

[PNG File , 163 KB - [resprot_v10i3e24534_app2.png](#)]

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Abbreviations

CBT: cognitive behavioral theory
FFMQ: Five Facet Mindfulness Questionnaire
HNRU: Human Nutrition Research Unit
MVP: My Viva Plan
NRF: nutrient rich food
REDCap: Research Electronic Data Capture

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Protocol

Evaluation of a New Personalized Health Dashboard in Preventive Child Health Care: Protocol for a Mixed Methods Feasibility Randomized Controlled Trial

Miriam Weijers^{1,2}, MSc, MD; Frans Feron², PhD, MD; Jonne van der Zwet², PhD, MD; Caroline Bastiaenen³, PhD

¹Department of Preventive Child Health Care, Municipal Health Services, South Limburg, Heerlen, Netherlands

²Department of Social Medicine, Faculty of Health, Medicine and Life Sciences, Care and Public Health Research Institute, Maastricht University, Maastricht, Netherlands

³Department of Epidemiology, Faculty of Health, Medicine and Life Sciences, Care and Public Health Research Institute, Maastricht University, Maastricht, Netherlands

Corresponding Author:

Miriam Weijers, MSc, MD

Department of Preventive Child Health Care

Municipal Health Services

South Limburg

Het Overloon 2

Heerlen, 6411 TE

Netherlands

Phone: 31 6 4644 2957

Email: miriam.weijers@ggz.nl

Abstract

Background: A new dashboard, the 360°CHILD-profile, was developed to adopt personalized health care within preventive child health care. On this profile, holistic health data are visualized in a single image to provide parents, adolescents, and caregivers direct access to a manageable résumé of a child's medical record. Theoretical ordering, conforming to "International Classification of Functioning, Disability and Health for Children and Youth", guides clinical reasoning toward the biopsychosocial concept of health. It is yet unknown if and how this promising tool functions in practice, and a variety of feasibility questions must be addressed.

Objective: This paper describes the design and methods of a feasibility randomized controlled trial (RCT), with the aim of evaluating the RCT's feasibility (recruitment, response, measure completion, and intervention allocation) and 360°CHILD-profile's feasibility (usability and potential effectiveness).

Methods: A pragmatic mixed methods study design was chosen, starting with an RCT to measure feasibility and health literacy in 2 parallel groups (1:1). Qualitative research will then be used to understand and explain quantitative findings and to explore the stakeholders' perspectives on the potential of the 360°CHILD-profile. Participants will include child health care professionals (n≥30), parents (n≥30), and caregivers (n≥10) of children who experience developmental problems (age 0-16 years). Children will only be able to participate if they are older than 11 years (adolescents, n≥10). The 2 groups included in the study will receive standard care. The experimental group will additionally receive personalized 360°CHILD-profiles.

Results: After an intervention period of 6 months, quantitative outcomes will be measured, analyzed (descriptive feasibility statistics and preliminary between-group differences) and used to purposively sample for semistructured interviews.

Conclusions: Study results will provide knowledge for building theory on the 360°CHILD-profile and designing future (effect) studies.

Trial Registration: Netherlands Trial Register NTR6909; <https://www.trialregister.nl/trial/6731>

International Registered Report Identifier (IRRID): DERR1-10.2196/21942

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KEYWORDS

child health services; prevention; control; personalized health care; international classification of functioning; disability; health; patient; access to records; personalized; child; feasibility

Introduction

To more effectively address the increasing burden of preventable chronic diseases, it is a prerequisite for current reactive health care (treatment after a diagnosis) to make the transition to personalized health care (PHC) [1]. According to Snyderman [2], PHC stands for a lifetime, holistic approach of proactively offering predictive, preventive, personalized, and participatory care. The different PHC concepts can and must be introduced in practice as soon as possible, but it appears to be a challenging task to effectuate such a new approach within health care [2,3].

Dutch preventive child health care (CHC), as part of public health, offers a unique platform to adopt PHC in the short term. CHC proactively monitors children's development and health to detect early deviance from normal variance and diseases or symptoms which cannot yet be clustered to a diagnosis. To fully apply PHC within the preventive CHC approach, a shift is needed toward prediction and prevention in the very early stages of disease progression when symptoms may not even be present [4,5]. To perform early detection and act upon disease progression is not an easy task because health processes are complex. The biopsychosocial model of health shows that health is a result of lifelong, multidimensional interactions between many biological–genetic characteristics and environmental factors. Therefore, to predict and protect health, insight into a broad set of health determinants is required. Critical to implementation of PHC is thus the availability and accessibility of high-quality, relevant lifetime health data.

From birth on, CHC collects health data about the child and environment, which are stored in an electronic medical dossier (EMD). However, accessibility of data is profoundly hindered due to the actual structure of EMDs, and thus support for the complex clinical reasoning process is insufficient [6,7]. It is not possible to generate an adequate overview of registered data in coherence with the relevant theoretical concepts (ie, the biopsychosocial model) [8]. As a result, much of the CHC-data that are highly relevant to understanding the complex processes underlying health are not available within the timeframe of CHC visits or other consultations with caregivers and parents.

To address this problem, a 360°CHILD-profile (Figure 1), which visualizes health information about the child and environment in a single digital image, has been originally developed and examined within daily practice of the Dutch CHC system [9].

Relevant CHC data, visualized on the 360°CHILD-profile, are theoretically ordered according to the “International

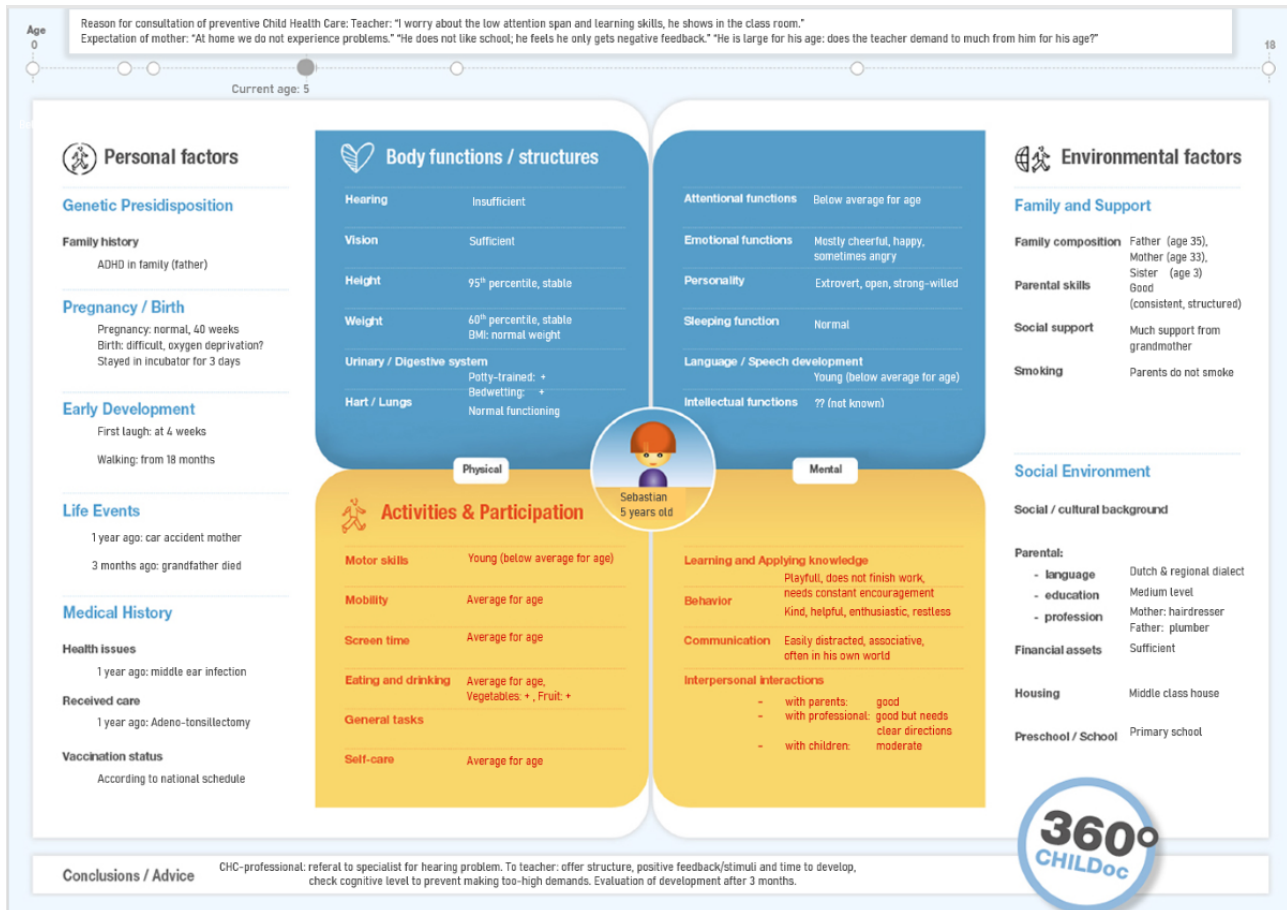
Classification of Functioning, Disability and Health for Children and Youth” (ICF-CY) [10]. The ICF-CY fits the CHC context and PHC concepts, as it is built on the integrated biopsychosocial approach of health and describes a broad variety of individual characteristics and environmental factors in concrete, neutral (if not positive) formulations [10]. The 360°CHILD-profile was developed as a dashboard that provides a quick, systemic, and comprehensible representation of a child's individually unique set of health determinants (protective and risk factors).

The goal of the 360°CHILD-profile is to provide direct access to a manageable résumé of holistic health information stored in the EMD to CHC professionals, parents, and adolescents, and to naturally guide thought processes in coherence with the chosen theoretical perspective (PHC). This dashboard supports health literacy in a way that can empower parents and adolescents to cocreate personalized plans for managing their (children's) health, in partnership with caregivers [11,12].

From the very start of the 360°CHILD-profile's development and research project (2012), parents, adolescents, and CHC professionals have been actively involved. Formal ideas for designing the profile's first drafts were generated, and pilot studies showed positive reactions of stakeholders for the comprehensibility, relevance, and acceptability of the design [9]. Promising results were generated in another study related to the 360°CHILD-profile's reliability and validity when used by CHC medical doctors to assess child functioning [13]. In 2018, data visualization designers and researchers used their expertise and gained input from stakeholders on CHC context, usability, and user experience to redesign the 360°CHILD-profile [9].

The current state of this newly developed 360°CHILD-profile offers a promising, online dashboard that is ready to be introduced into CHC practice. If and how it will actually function within daily practice is yet unknown, and it is foreseen that the evaluation of effectiveness in the multidisciplinary and preventive CHC context will be complex. Therefore, a pragmatic feasibility RCT will be performed to refine our practice-derived theory on the 360°CHILD-profile's feasibility and potential effectiveness and to build a rationale for designing future (effect) studies (including outcome measures and sample size calculations) [14,15]. The aim of this paper is to describe the design and methods of this study that will be performed within CHC.

Figure 1. The 360°CHILD-profile: representation of a child's health information available in the CHC electronic medical dossier, based on the "International Classification of Functioning, Disability and Health for Children and Youth" [10]. Child's name, gender, and age appear in the center; the most recently acquired data about the child's body functions and structures in physical and mental aspects appear in the blue area; and information on activities and participation appear in the yellow area. Data about genetic predisposition and history (medical, developmental, and life events) are listed in the left column, and information about environmental factors are in the right column. On top of the 360°CHILD-profile, a timeline is provided with bullet points at which ages the child visited CHC, and a CHC and a 360°CHILD-profile (snap-shot) is generated. At the bottom of the 360°CHILD-profile, conclusions and advice from the most recent CHC visit are presented. CHC: child health care.



Methods

Study Design

For this pragmatic feasibility RCT, a sequential mixed methods design was chosen. First, quantitative research will be performed. Within the limitations of a feasibility study [16], an RCT will be executed with 2 parallel groups (experimental and control). Qualitative research will then be performed to understand and explain the quantitative findings and to explore the 360°CHILD-profile's potential benefit in CHC practice [17-19]. The study objectives will be to evaluate 2 types of feasibility: that of the 360°CHILD-profile and that of the RCT.

- (1) The 360°CHILD-profile feasibility evaluation will include the following: usability, including the frequency and profundity of 360°CHILD-profile use during contacts between CHC professionals, parents, adolescents, and other caregivers; and the perspective of parents, adolescents, CHC professionals, and other caregivers on quantitative findings, requirements for the 360°CHILD-profile's use within CHC, and potential benefit and effectiveness.
- (2) The RCT feasibility evaluation will include the following: recruitment, retention, and response rates; acceptance of and compliance to allocated interventions;

measurement completion and protocol deviations; health literacy measurement, including the variance of parent's satisfaction on health literacy in the total and in each separate group, and a preliminary estimation of the between-group differences; the perspective of parents, adolescents, and CHC professionals on hindering and promoting factors for recruitment, retention, and response rates, acceptance and compliance to allocated intervention, measurement completion, and preliminary differences on health literacy.

Study Population and Sample Size

The study population will mainly consist of parents and CHC professionals (nurses and medical doctors) who are involved in the care of the parent's child (age 0-16 years) experiencing emerging problems. Adolescents (age >11 years) and other involved caregivers can also be included as participants, but children under the age of 12 years will not themselves participate. If parents or adolescents cannot comprehend the written health information (due to a language barrier or other reasons), they will not be included in this study.

For the quantitative phase, we aim to recruit 30 parents, 30 CHC professionals, 10 adolescents, and 10 other caregivers. For

feasibility studies, in which outcome parameters like recruitment, response rates, and variance in the outcomes of questionnaires (SD) are measured, a sample size of 60-70 participants is justified [16,20,21]. For qualitative research with purposive sampling, it is estimated that saturation will be reached after including 20-30 participants (7-10 participants per target population; ie, parents and CHC professionals) [19,22].

Procedure

All nurses and medical doctors working for CHC organizations in the Dutch region of South Limburg will be asked to participate. After providing informed consent, volunteers will attend a 2-hour long instructional workshop to receive information about the 360°CHILD-profile, study procedures (inclusion and randomization), and outcome measures.

Participating CHC professionals will identify and approach eligible parents during CHC visits and eligible caregivers at the moment they become involved in the care of the parent's children. If parents or caregivers are interested and give permission to be contacted by the researcher, researchers will start the information and informed consent procedures and enroll participants in the study after given permission.

At the end of the quantitative phase, quantitative findings will be used for purposive sampling for qualitative research to obtain a variety of perspectives from parents and caregivers and to reach a broad interpretation of the quantitative findings [19,22]. From each group within the study population (parents, adolescents, CHC professionals, and involved caregivers), 2 participants will be invited for each round of interviews. After analysis of the conducted interviews, both quantitative and qualitative findings will be used to select participants for the next round to enrich characteristics and opinions.

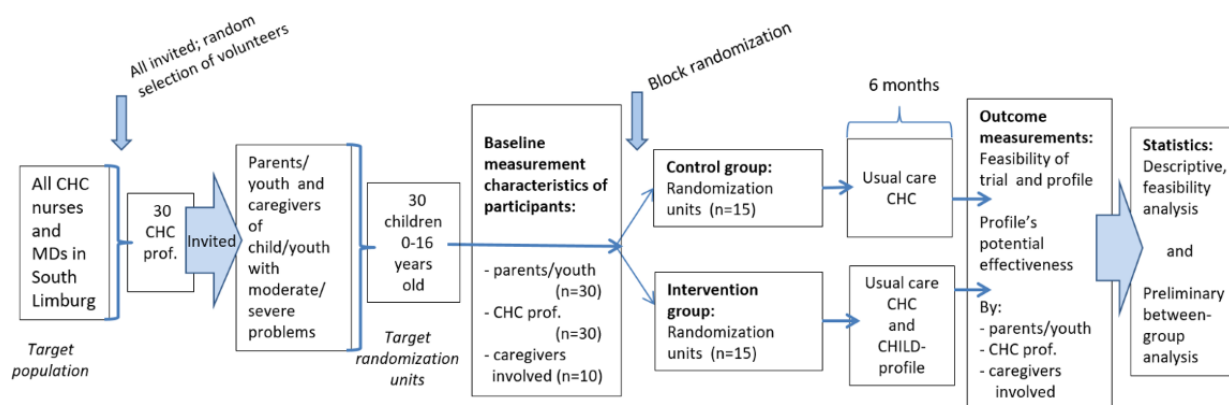
Randomization and Concealed Allocation

After parents sign informed consent, they will be allocated to 1 of 2 parallel groups in a 1:1 ratio (experimental or control group) according to centralized randomization (by an independent administrator based on a protocol). The randomization plan with central block randomization (blocks of 4 and 6) will be generated beforehand by CB (not involved in the enrolment and intervention) using an online randomization system. Each phase (enrolment, randomization, quantitative outcome measurement, and analysis) will be performed independently from the others (concealed allocation), and researchers will be blinded to randomization and allocation. Parents and professionals will be, as much as possible, kept unaware of the detailed study aims related to the allocation.

Experimental and Control Intervention

For a period of 6 months, children of the participating parents in both groups will receive usual care. Additionally, for 50% of the children (the experimental group), CHC information from the EMD will be electronically transferred to a personalized 360°CHILD-profile. Directly after baseline measurement, the profile will be available in the EMD for CHC professionals to discuss with the parents or adolescents during the visit. After this visit, the profile also will be made accessible online for the parents or adolescents. During the 6-month follow-up period, participants will be able to consult the profile and use it to contact the caregivers whenever they want. The individual child's health data, as presented on the profile, will not be collected and used as scientific data in the study. After the last study measurements are completed, a personalized 360°CHILD profile will also be generated for parents or adolescents in the control group (outside the context of the study). A flowchart of the RCT's study protocol is provided in [Figure 2](#).

Figure 2. Flowchart of the randomized controlled trial's protocol. CHC: child health care; MD: medical doctor; prof: professional.



Measures and Measurements

Questionnaires will be used to obtain baseline measurements of the following characteristics: for participating adolescents and children, information on age, gender, and level of functioning and experienced problems as indicated by CHC professionals will be measured; for parents, information on age, gender, country of birth, educational level, perspective on their

child's health and development, parenting situation, and number and age of children will be collected; for CHC professionals and other caregivers, information on discipline, educational level, experience, and perspective on the use of information technologies in health care will be collected.

An overview of the baseline measures regarding population characteristics are presented in [Table 1](#).

Table 1. Baseline measures for population characteristics.

Measures	Measuring	Age group	Answer options	Reference
STEP ^a	Standardized professional's rating of child's functioning, experienced problems, quality of environment, and needed care	0-16	5-point scale	[23]
CGAS ^b	Professional's rating of child's functioning	0-16	Continuous scale	[13,24]
PEDS ^c	Parents' questions and concerns about child's development	0-6	3-point scale and open ended	[25]
SDQ ^d	Parents' and adolescents' perspective on psychological attributes	3-16	3-point scale	[26,27]
NOSIK ^e	Parents' perspective on parenting stress ^f	2-13	6-point scale	[28]

^aSTEP: Standaard Taxatie Ernst Problematiek (only available in Dutch).

^bCGAS: Children's Global Assessment Scale.

^cPEDS: Parents' Evaluation of Developmental Status.

^dSDS: Strengths and Difficulties Questionnaire.

^eNOSIK: Nijmeegse Ouderlijke Stress Index-Korte versie.

^fAs derived from the Parenting Stress Index-Short Form

Measurements will be conducted 6 months after baseline to measure the qualitative and quantitative outcomes of the 360°CHILD-profile's and RCT's feasibility.

The 360°CHILD-profile's Feasibility

The evaluation of the 360°CHILD-profile's feasibility is described in this section. Quantitative outcomes on feasibility will include the following: frequency of use of the 360°CHILD-profile by CHC professionals during contacts with parents or adolescents, as registered by CHC professionals; the profundity in which the 360°CHILD-profiles are used during CHC visits, as indicated by CHC professionals on a questionnaire (using questions with answer options on a categorical scale).

Qualitative outcome (semistructured interviews with parents, adolescents, CHC professionals, and other caregivers) will be collected for the follow purposes: to contextualize and further inform the understanding of quantitative findings on 360°CHILD-profile's usability; and to explore the expectations of parents, adolescents, CHC professionals, and other caregivers regarding the 360°CHILD-profile's potential benefits in CHC practice.

RCT Feasibility

Evaluation of the RCT feasibility will occur in both group and is described in this section.

The quantitative measurements will include the following: recruitment rate (the percentages of volunteers versus invited and eligible participants); retention rate (the percentage of participants completing the study versus the participants that started); response rates (the percentages of participants per discipline who filled in and validated the questionnaire versus the number of participants who were requested); compliance to allocated intervention (the percentage of CHC professionals in the experimental group who used the 360°CHILD-profile during a CHC visit); measure completion (the percentages of completed measures versus incomplete measures and description of missing data); protocol deviations (the description of problems

encountered and eventual adaptations to the protocol for properly addressing these problems); health literacy.

Health literacy will be evaluated using the validated Dutch version of the Consumer Quality Index (CQI). The CQI is based on the Consumer Assessment of Healthcare Providers and Systems (CAHPS) and is applicable for parents of children aged 0-18 year who visit CHC [29]. The validated CQI includes questions about accessibility, ability to understand, completeness and applicability of received care, and health information and advice, with answer options on a 2-, 3-, or 4-point scale (subscale reliability: Cronbach α =.75-.82) [30]. Additionally, relevant questions from "Supplemental Items for the CAHPS on Health Information Technology" were translated from English to Dutch and incorporated into the CQI questionnaire [31]. The research team developed additional questions to ensure measurement of all dimensions of the construct's "access to healthcare and health information" [32]. The dimensions we indicated as relevant for the CHC context and this study are availability, accommodation, accessibility, and acceptability. Affordability is not relevant in this context because CHC care is offered for free to all children and parents. This set of additional questions (n=6) with answers options on a 5-point scale will be used for the first time, and no information on the diagnostic parameters is available yet.

The qualitative measurements for RCT feasibility will include semistructured interviews with parents, adolescents, CHC professionals, and other caregivers, and will be performed for the following purposes: to contextualize and further inform the quantitative findings on recruitment, retention and response rates, compliance to allocated intervention, measurement completion, and health literacy; to explore CHC professionals' experiences during recruitment of parents and adolescents, and participants' satisfaction regarding their study participation and allocated intervention and perspective on requirements for a future randomized trial.

All semistructured interviews will be in person and audio-recorded. Recordings will be transcribed, and the collected data will be coded (participants will be allocated a participant

number code to relate data to this code). Records will be stored in a locked place on the server separate from the other study data. Only the investigator collecting the data will have access to this documentation.

Statistical Analysis

Baseline characteristics of all participants will be presented using descriptive statistics (mean, SD, or frequencies and range) in a table. Data of parents, adolescents, and children will be presented for the total group and for both randomized groups separately.

Quantitative Outcome Data

Descriptive analysis will be performed to present outcomes on the 360°CHILD-profile's and RCT's feasibility (usability). The descriptive analysis of the 360°CHILD-profile will include the following: the frequency in which the 360°CHILD-profile is used, for which the mean and variability will be calculated; and the profundity of use of the 360°CHILD-profile during a CHC visit, which will be presented as proportions per category.

The descriptive analysis for RCT feasibility will include the following: recruitment, retention, and response rates, compliance to allocated intervention, measurement completion, and missing data, which will be presented as logistic data and proportions; protocol deviations, which will be described using text; outcome on health literacy, including descriptions for the total sample and for each group, with continuous measures (presented as mean, SD, and CI) and categorical measures (presented as proportions).

Statistical between-group analysis will be performed to preliminarily calculate (estimates of) differences between groups (and 95% CIs), using linear mixed models. Potential confounders (for example health status, age, and education) will be evaluated and, if necessary, adjusted.

Qualitative Outcome Data

Analysis of each transcript will be performed by 2 independent researchers. Discrepancies will be discussed by the research team and consensus will be reached concerning codes based on expert agreement. The analysis process will include thematic analysis with open coding at the start followed by axial coding. In each phase of the analysis process, data will be reviewed using constant comparative methods. The units that will be used to describe themes and concepts can be words, sentences, or stories. Cycles of data collection and analysis will be repeated until data saturation is reached according to our research goals.

Connection Between Quantitative and Qualitative Results

After quantitative results are described and interpreted, they will be used to refine or adjust research questions, purposeful sampling procedures, and data collection protocols of the qualitative phase. During qualitative analysis, data will be interpreted and described separately and in coherence with quantitative results to realize the advantages of mixing both research methods, which include complementarity, triangulation, and explanation of results.

We will discuss if and how the qualitative results further the understanding or explanation of the quantitative findings and

how to formulate overall conclusions and recommendations regarding theory on the 360°CHILD-profile and the rationale for designing future (effect) studies within CHC.

Results

The intended timeline for achieving the targeted results includes the acceptance for funding (December 2016), approval by The Medical Ethics Committee of the Maastricht University Medical Centre (no. METC azM/UM 2017-0089; July 2017), registration in the Netherlands National Register (6909; January 2018), enrolment of participants (May 2018 to September 2019), quantitative outcome data collection (March 2019 to September 2020), and qualitative data collection (October 2019 to February 2021). The results of the presented study will be available before the end of 2021.

Discussion

This pragmatic quantitative–qualitative study will comprehensively evaluate the feasibility of the newly developed 360°CHILD-profile and the feasibility of conducting an RCT within the preventive setting of the CHC.

This practice-derived dashboard is new in providing a holistic and structured display (in accordance with the ICF-CY framework) of the large and complex electronic CHC data sets [13]. Earlier pilot studies, application tests, and qualitative user tests have already shown promising results for the relevance, comprehensibility, acceptability, reliability, and validity of the 360°CHILD profile [9,13]. However, these pilots and validation tests were all performed during sessions guided by researchers in order to optimize technical and visual aspects and to increase the likelihood of usability and effectiveness. Thus, this feasibility study will generate first results on usability of this promising tool within the real-life CHC practice. This study will also generate indispensable knowledge on how to test the efficacy of this practice-derived innovation in the CHC context and is a necessary and sound intermediate step in the overall multiyear mixed methods research project [15,16].

From a pragmatic viewpoint, we searched for design options that fit current research questions and CHC context. A mixed methods design with a sequential explanatory (quantitative–qualitative) setup was chosen to enable testing our a priori, practice-based hypotheses and to give voice to parents, adolescents, and caregivers to refine theory. The pragmatic approach of the feasibility RCT enables the execution of a randomized trial within the preventive and multidisciplinary field of work and generation of results that fit this context [17]. The investment of time by CHC professionals is limited as much as possible; only a short training period is needed, each professional will need to recruit only 1–2 parent(s), and professionals are left close to daily practice during the “intervention” period (care as usual). Furthermore, CHC professionals in the experimental group do not have to drastically change their working method; they will present the personalized profile to parents and adolescents, but after that, all participants are free in choosing how (often) to use it. The between-group difference might seem rather subtle, but we

expect it will have substantial impact. Our hypothesis is that the availability of the dashboard will automatically lead to efficiency (there is less wasting of time to search for data in the EMD and better quality of health literacy and early prevention of disease progression). Moreover, we expect that the theoretical structure of the profile will intuitively guide clinical reasoning in line with the context of CHC and PHC.

Information bias will be reduced by the centralized randomization, blinding of researchers for randomization, and keeping participants unaware of the detailed study aims.

Children and their parents have been chosen as the level of randomization (and not CHC professionals) to avoid bias due to differences in professionals' working methods, characteristics, and level of experience. Contamination is avoided by virtue of the fact that, for CHC professionals in the control group, it is not possible to obtain an overview of the holistic health data from the EMD, as it is simply not available.

From the original study population, a heterogeneous population of participants will be selected for semistructured interviews to provide an in-depth insight into a broad spectrum of perspectives [33]. Interpretation of quantitative and qualitative data will be in coherence with each other, which strengthens the study's internal validity and deepens our understanding of the findings.

This pragmatic study will ensure adequate evaluation of the currently relevant feasibility questions, and the findings will direct our decisions concerning the 360°CHILD-profile's implementation in Dutch CHC practice and the design of future (effect) studies. The eventual goal of this research project is to bridge the gap between the technical design of EMDs and clinical practice to enable EMDs to efficiently support CHC in its preventive tasks and give parents access to the EMD summaries. Therefore, CHC and parents can monitor health, detect deviation of normal variance and disease progression as early as possible, and cocreate preventive strategies to protect and promote children's health—health plans that will fit each individually unique child.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Final decision from Dutch funding agency ZonMW.

[[PDF File \(Adobe PDF File\), 323 KB - resprot_v10i3e21942_app1.pdf](#)]

Multimedia Appendix 2

Report of first peer-reviewer from Dutch funding agency ZonMW.

[[PDF File \(Adobe PDF File\), 75 KB - resprot_v10i3e21942_app2.pdf](#)]

Multimedia Appendix 3

Report of second peer-reviewer from Dutch funding agency ZonMW.

[[PDF File \(Adobe PDF File\), 78 KB - resprot_v10i3e21942_app3.pdf](#)]

Multimedia Appendix 4

Translation of peer-reviewer reports for the grant proposal and final decision from Dutch funding agency ZonMW.

[[DOCX File, 27 KB - resprot_v10i3e21942_app4.docx](#)]

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Abbreviations

CAHPS: Consumer Assessment of Healthcare Providers and Systems

CHC: child health care

CQI: Consumer Quality Index

EMD: electronic medical dossier

ICF-CY: International Classification of Functioning, Disability and Health for Children and Youth

PHC: personalized health care

RCT: randomized controlled trial

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Protocol

Effectiveness of a Postpartum Text Message Program (Essential Coaching for Every Mother) on Maternal Psychosocial Outcomes: Protocol for a Randomized Controlled Trial

Justine Dol¹, MSc; Megan Aston², PhD; Douglas McMillan³, MD; Gail Tomblin Murphy⁴, PhD; Marsha Campbell-Yeo², PhD

¹Faculty of Health, Dalhousie University, Halifax, NS, Canada

²School of Nursing, Faculty of Health, Dalhousie University, Halifax, NS, Canada

³Department of Pediatrics, Faculty of Medicine, Dalhousie University, Halifax, NS, Canada

⁴Nova Scotia Health, Halifax, NS, Canada

Corresponding Author:

Justine Dol, MSc

Faculty of Health

Dalhousie University

6299 South St

Halifax, NS, B3H 4R2

Canada

Phone: 1 902 470 2640

Email: Justine.dol@dal.ca

Abstract

Background: Women experience changes both physically and psychologically during their transition to motherhood. The postnatal period is a critical time for women to develop maternal self-efficacy. Mobile health interventions may offer a way to reach women during this critical period to offer support and information. Essential Coaching for Every Mother is a text message program that seeks to educate and support women during the first 6 weeks postpartum.

Objective: The primary effectiveness objective is to compare the effectiveness of the Essential Coaching for Every Mother program on maternal psychosocial outcomes (self-efficacy, social support, postpartum depression, and postpartum anxiety) immediately after the intervention and 6 months postpartum, collectively as well as stratified by parity. The primary implementation objective is to evaluate the implementation extent and quality of the Essential Coaching for Every Mother program.

Methods: This will be a hybrid type 1 effectiveness-implementation randomized controlled trial. A total of 140 mothers-to-be or new mothers from Nova Scotia will be recruited and randomized to the intervention or control arm, stratified by parity. The intervention arm will receive the Essential Coaching for Every Mother program, which consists of 53 messages sent twice a day for the first 2 weeks and daily for weeks 3 through 6. The control group will receive usual care. Messages are personalized based on the infant's age and the woman's self-selected preference for breastfeeding or formula feeding and tailored with the infant's name and gender. Women can enroll in the program if they are ≥ 37 weeks pregnant or within 10 days postpartum, with the first message designed to be sent on the second evening after birth. The actual number of messages received will vary based on the timing of enrollment and the infant's date of birth. Participants will complete questionnaires assessing self-efficacy, social support, and postpartum depression and anxiety at baseline (enrollment after birth) and 6 weeks (postintervention) and 6 months postpartum. Implementation data will be collected throughout the trial, and evaluation feedback will be collected at 6 weeks from women who received the intervention.

Results: Recruitment for this study started on January 5, 2021, and is currently ongoing, with an anticipated date of recruitment completion of January 2022.

Conclusions: This study will assess the effectiveness of a postpartum text message program to improve maternal self-efficacy and social support while decreasing postpartum depression and anxiety. It will also shed light on the implementation effectiveness of the program.

Trial Registration: ClinicalTrials.gov NCT04730570; <https://clinicaltrials.gov/ct2/show/NCT04730570>

International Registered Report Identifier (IRRID): DERR1-10.2196/27138

KEYWORDS

text message; mobile health; postpartum education; self-efficacy; social support; postpartum anxiety; postpartum depression

Introduction

Background

During the postpartum period, women require support and information to ensure a smooth transition and adjustment to motherhood, which is reflected in both the World Health Organization's postnatal guidelines [1] and the Public Health Agency of Canada's maternity and postnatal care guidelines [2]. Worldwide, the postnatal period is often neglected in the provision of quality care [1,3]. During pregnancy, women are regularly monitored, especially during the third trimester with weekly or biweekly appointments, yet after they give birth the frequency of monitoring is significantly reduced to only once or twice in the first year, typically first around 6 weeks postpartum [4,5]. The amount and type of postpartum care that women receive for themselves and their infants depend on whether they are being followed by doctors or midwives, they are considered to have high needs, or they have identified health concerns for themselves or their infants [6].

Although the postnatal period provides an opportunity to educate and support new mothers, many women have reported not having enough information to help them in their transition to motherhood, resulting in challenges to their psychosocial adjustment [7,8]. While the postpartum period may be uncomplicated for some women, evidence suggests that others may struggle with low self-efficacy [9], feel isolated or struggle with low social support [9,10], and experience symptoms of anxiety and depression [10,11]. There is a need to develop and evaluate innovative approaches to educate and support women during this period to ensure that maternal psychosocial health needs are met and concerns are addressed in a timely manner. Evidence suggests that women are turning to online and mobile apps for sources of information during the perinatal period [12,13]. Therefore, there is an opportunity to develop a standardized, evidence-based mobile health (mHealth) intervention to address known concerns around maternal psychosocial adjustment to enhance their feelings of self-efficacy and social support while decreasing levels of postpartum anxiety and depression.

While postpartum mobile apps are also growing in prevalence, a recent systematic review identified 48 mobile apps of varying quality [14]. Also, mobile apps require access to data plans, rely on push notifications that may not be enabled, and are time consuming to build. On the other hand, one aspect of mHealth that shows significant promise is text messaging because of its cost-effectiveness, broad reach, and simplicity of use. There is some evidence that text messaging programs can enhance maternal and newborn outcomes and engage mothers during the postnatal period [15,16]. Existing postpartum text message programs focus on various postpartum topics—text4baby aims to improve perinatal health for women and their infants [17], MobileMums is focused on enhancing physical activity [18], and MumBubConnect's goal is to promote breastfeeding

[19]—yet no postpartum text message programs are currently available in Canada. The provision of timely health information can influence behaviors through repeated and relevant health messages [20]. Text messages can be sent, saved, and retrieved at any time [21], are able to be personalized and tailored, and can be provided through one- or two-way communication [22]. Therefore, a text message program was designed with low barriers to entry, low cost for participation, and ease of development and modification.

Our team developed Essential Coaching for Every Mother, an evidence-based postpartum text message program, with the goal of improving mothers' access to information about caring for themselves and their newborn during the immediate 6-week period after birth [23]. The program was developed through iterative testing with mothers and postpartum health care providers [23] and showed preliminary effectiveness and uptake during a pilot pre-post intervention study offered during COVID-19 [24].

Effectiveness Objectives

The primary effectiveness objective of this study is to compare the effectiveness of the Essential Coaching for Every Mother program to standard care on self-efficacy measured immediately after the intervention. The secondary objectives are (1) to compare the effectiveness of the Essential Coaching for Every Mother program to standard care on social support, postpartum anxiety, and postpartum depression immediately after the intervention; (2) to determine whether the effect on any outcomes differs based on parity (multiparous or primiparous); and (3) to compare any long-term impacts of the Essential Coaching for Every Mother program on the above outcomes at 6 months postpartum.

Effectiveness Hypotheses

The primary hypothesis is that the Essential Coaching for Every Mother program will result in higher self-efficacy for participants who receive the intervention compared with standard care. The secondary hypotheses are that (1) Essential Coaching for Every Mother will result in higher levels of social support, lower levels of postpartum anxiety, and lower levels of postpartum depression for those who receive the intervention compared with standard care; (2) there will be no difference based on parity on any of the psychosocial outcomes; and (3) changes in psychosocial outcomes will be maintained over time.

Implementation Objective

The implementation objective is to evaluate the implementation extent (ie, enrollment rate and timing, withdrawal rate, number of messages received) and quality (ie, satisfaction, barriers, suggestions for improvement) of the Essential Coaching for Every Mother program.

Methods

Study Design

This study will be a 2-group, stratified, parallel-arm, hybrid type 1 effectiveness-implementation randomized controlled trial. Through the use of an effectiveness-implementation design, it is possible to evaluate intervention effectiveness while simultaneously evaluating real-world implementation to guide future development and revisions [25]. The intervention will be compared with standard care that is currently being provided across Nova Scotia, stratified by parity.

Ethics Approval

The study has been approved by the IWK Health Research Ethics Board (#1024984) and the Nova Scotia Health Research Ethics Board (#1026534) and is registered with the clinicaltrials.gov Protocol Registration System (NCT04730570). The CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and onLine TeleHealth) checklist [26] will be followed to improve the reporting as an eHealth intervention trial. In reporting the process evaluation, the Template for Intervention Description and Replication (TIDieR) checklist and guideline will be used [27,28]. The TIDieR checklist offers a standardized way to describe the implementation and document any deviations that arise, which allows for not only replication but also clear reporting for comparison of interventions [27].

Setting

This study is being conducted across Nova Scotia, Canada. In 2017, Nova Scotia had a total of 8197 live births [29]. Currently in Nova Scotia and across Canada broadly, there is no standardization of delivery of postpartum care within or between provinces [6]. Thus, there is a need for interventions targeting the postnatal period to enhance the postpartum experience for mothers in Nova Scotia.

Inclusion Criteria

Participants will be recruited antenatally and postnatally. To enroll antenatally, participants must (1) be at least 37 weeks pregnant; (2) have daily access to a mobile phone with text messaging capabilities; (3) be ≥ 18 years of age; (4) live and give birth in Nova Scotia; and (5) speak and read English. To enroll postnatally, participants must (1) have an infant younger than 10 days of age; (2) have daily access to a mobile phone with text messaging capabilities; (3) be ≥ 18 years of age; (4) live and gave birth in Nova Scotia; and (5) speak and read English.

Participants will be excluded if (1) their newborn dies or is expected to die prior to leaving the hospital; (2) they have no access to a mobile phone, either personal or shared; (3) they are unwilling to receive text messages; (4) they decline to participate or withdraw; or (5) they previously participated in the development or feasibility phase of this project.

Recruitment

A multipronged approach will be used to recruit women who are at least 37 weeks pregnant or within 10 days postpartum.

All recruitment will occur remotely with no in-person promotion. The primary methods will be social media advertisements (eg, posting on relevant parent groups on Facebook, paid advertisements on Facebook) as well as study posters across the province (eg, on the Family Newborn Unit at IWK Health, in perinatal centers, in family medical offices, etc). Additional sources of outreach that may be used include promotion through public health, family resource centers, media outreach, posters in public places that pregnant and new parents frequent, and word of mouth.

While the text messages are one-way only, if a participant responds to a message with a question for clarification, the principal investigator or research team member may respond to provide clarification only. For example, if a participant asks if they will receive reminder messages, a brief message will be provided confirming that reminder messages will be sent. If there are requests for advice on their care or that of their baby, mothers will be referred back to their health care provider through a standardized message sent if a participant responds unexpectedly during the program.

Screening and Baseline

Interested participants will contact the research team via text message to complete the automatic remote eligibility screening process. All participants will receive a welcome message as well as details about the study and what the study will entail. During the antenatal recruitment process, the woman's phone number, first name, and due date will be collected via TextIt [30]. This information is required to ensure that follow-up messages are sent to the woman via her mobile device based on her due date.

During the antenatal screening process, participants will be screened for eligibility, and eligible participants will be informed of the need to send a text within 10 days after giving birth to be enrolled in the study. Women who have not yet given birth are sent messages at 39 weeks, 40 weeks, 41 weeks, and 42 weeks or until enrolled or withdrawn to remind them of the need to text the word "delivered" after giving birth. Participants who initiate contact before 37 weeks will be asked if they want to be sent follow-up messages once they reach 37 weeks until the sample size is reached.

Once a woman gives birth or enrolls after giving birth, she will be asked screening questions to ensure eligibility and determine parity for stratification. Additional details including the newborn's name, preferred gender pronoun for the infant, infant's date of birth, and parity will be collected at that time. Once stratified, participants will be randomized and informed of their group allocation. Participants who are randomized to the intervention group will be asked their preference on breastfeeding and formula feeding messages. All participants will be asked to complete the consent form and baseline survey. To remind participants to complete the survey, reminder text messages will be sent via TextIt every other day for 2 weeks (a maximum of 6 total messages) or until the survey is completed. An email will be sent as a final reminder to participants who have not yet completed the survey after day 14. If an email address was not provided, an expanded text message will be sent on day 14 instead. Participants will also be informed that

they may message “STOP” to withdraw from the study at any time. If a participant withdraws from the study, they will not receive any further messages nor will they be asked to complete any future surveys. Participants who complete the baseline survey will receive an electronic gift card worth Can \$15 (US \$11.97).

Randomization

Using a 1:1 allocation, participants will be randomized into either the intervention group or the control group using the “split randomly” function within the TextIt platform [30]. This function randomly passes contacts through approximately equally distributed pathways in the flow and will allocate them to receive either the intervention or the control condition. Randomization will occur after a participant has given birth. Participants will be stratified into 2 groups based on parity (primiparous and multiparous) prior to randomization.

Follow-Up Assessments

At both 6 weeks and 6 months postpartum, all participants in both groups will be sent a text message asking them to complete a follow-up survey. Participants will be asked to provide consent, and once consent is given, they will start the survey. Participants who complete the follow-up surveys will receive an electronic gift card worth Can \$15 (US \$11.97) for each survey. To remind participants to complete the survey, reminder text messages will be sent via TextIt every other day for 2 weeks (a maximum of 6 total messages) or until the survey is completed. An email will be sent as a final reminder to participants who have not yet completed the survey after day 14. If an email address was not provided, an expanded text message will be sent on day 14 instead.

Blinding

Because of the nature of the Essential Coaching for Every Mother program, blinding of participants is not possible, and therefore participants will be informed of their group allocation. To minimize personnel blinding related to data collection, no hospital staff will be informed of participants’ involvement in the study. This is possible because Essential Coaching for Every Mother is sent to the participant’s personal cell phone, with no in-person component to the intervention. The lead researcher will be aware of participants’ allocations and will be responsible for summarizing data but will not be involved in the randomization procedure, which will occur directly in the TextIt platform. Additionally, there will be no interaction between the participants and anyone on the research team because everything occurs remotely via a previously set up process, reducing any risk of personnel or outcome assessor bias.

Sample Size

The sample size was calculated based on the primary outcome of self-efficacy using the findings from our feasibility study [24], which showed a mean difference in self-efficacy scores between baseline and 6-week follow-up of 3.78 (SD 4.5). Therefore, with stratification by parity and a moderate intraclass correlation of $\rho=0.2$, a sample size of 30 participants per cluster and 60 participants per group (120 total participants) is required to be powered for analysis at the level of parity. In the feasibility study, there was an incompleteness rate of 15.5%; thus, the

estimated sample size will be increased by 15% to 69 participants per group, rounded up to 70 participants. In total, 140 participants will be enrolled in the study.

Program Content and Design

Text Messages

Essential Coaching for Every Mother consists of 53 standardized text messages that provide evidence-based information related to caring for a newborn and maternal mental health that all new mothers should know. Messages will be sent to participants from birth to 6 weeks postpartum, with 2 messages per day in the first 2 weeks and a daily message in weeks 3 through 6. The following topics are covered in the messages: postpartum anxiety, postpartum depression, maternal self-care, postnatal follow-up, breastfeeding or formula feeding, feeding, infant concerns, cord care, well-baby care, normal development, crying, and safe sleep. Women who receive the messages will be able to self-select breastfeeding or formula feeding messages. The TextIt platform will be used to program and schedule the messages [30], and Twilio will be used as the gateway service that offers virtual phone numbers and short codes that send and receive messages on behalf of the TextIt account [31].

Intervention Group

Participants in the intervention group will receive the standard in-person care in the hospital in which they give birth. After enrollment into the study, participants will start receiving messages until 6 weeks postpartum. The messages will be sent automatically based on the age of the infant. Participants in the intervention group will receive Essential Coaching for Every Mother as early as the evening of the second day after giving birth. This could be as early as 17 hours after birth (if a woman delivered at 11:59 the night before) or as late as 41 hours (if a woman delivered at midnight). If a participant enrolls after the messages are designed to start, they will start the message flow based on when they gave birth. Messages are sent at 10 AM and 5 PM during the first 2 weeks and at 10 AM daily after that. This time was recommended by both women and health care providers during the development of the intervention [23].

Control Group

Participants in the control group will receive the standard in-person care in the hospital in which they give birth. Women in the control group will not receive any study text messages but are not limited in their ability to seek additional postpartum support outside of the study. Data will be collected for both groups regarding postpartum support sought.

Study Measures

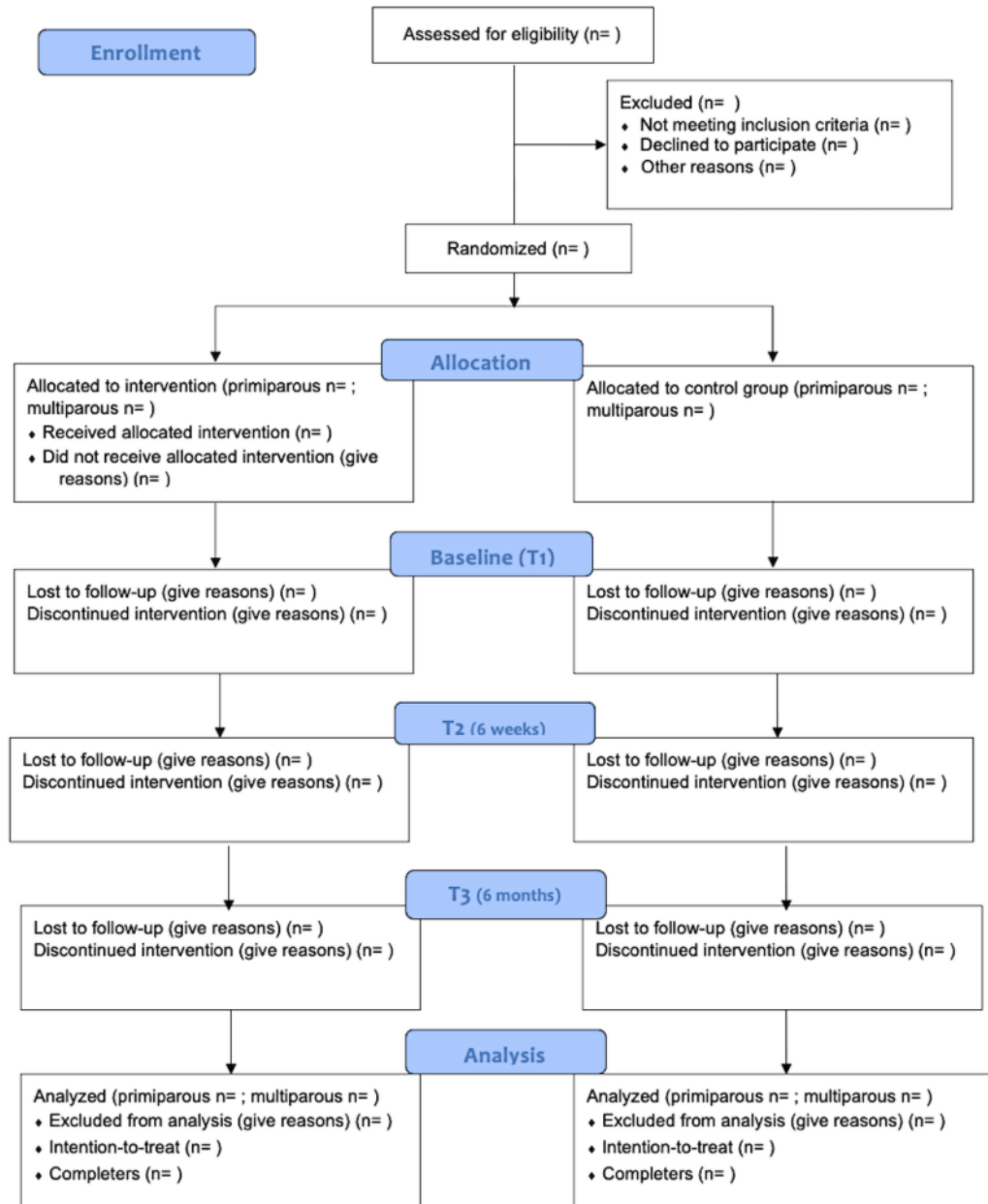
The same data will be collected from all participants, regardless of their group allocation, via self-reported online surveys through Research Electronic Data Capture (REDCap) hosted at IWK Health. Upon enrollment and at 6 weeks and 6 months postpartum, all participants will be sent a text message with a link to a REDCap survey. Background demographics will be collected at baseline on outcomes such as maternal age, occupation, marital status, and education level. At 6 weeks, a follow-up survey will be conducted to collect data on whether mothers had any postnatal contacts for themselves or for their

infant, health concerns, health information seeking, infant outcomes, the birth journey (including any intensive care stays), and infant feeding behavior. At 6 months, information on postnatal care and infant feeding behavior will be collected. Implementation data will be collected throughout the trial, and

evaluation feedback will be collected at 6 weeks from women who received the intervention. [Table 1](#) provides details of the data collected at each of the outcome assessment time points, and [Figure 1](#) outlines the CONSORT flow diagram.

Table 1. Data collected at the study outcome assessment time points.

Data collected	Enrollment	Baseline (T1)	6-week follow-up (T2)	6-month follow-up (T3)
Enrollment				
Eligibility screen	✓			
Informed consent		✓	✓	✓
Randomization	✓			
Assessments				
Demographics		✓		
Self-efficacy		✓	✓	✓
Social support		✓	✓	✓
Postpartum anxiety		✓	✓	✓
Postpartum depression		✓	✓	✓
Postpartum care and adjustment			✓	✓
Delivery experience			✓	
Feeding experience			✓	✓
Health information seeking			✓	
Implementation				
Quality			✓	
Extent	✓	✓	✓	

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

Effectiveness Outcomes

The primary outcome of self-efficacy will be measured using the Karitane Parenting Confidence Scale (KPCS) [32]. This 15-item scale assesses the perceived self-efficacy of mothers of infants up to 12 months of age and has acceptable internal consistency (Cronbach $\alpha=.81$) and test-retest reliability ($r=0.88$) [32]. A cutoff score of ≤ 39 (out of a possible 45) was determined to indicate a clinically low level of perceived parenting self-efficacy [32]. Additionally, a reliable change index of ≥ 6 was considered a significant change in their level of parental self-efficacy. Therefore, parents can be considered to have a high level of parenting self-efficacy if they either have a score above 39 or improve their score by 6 points, while still less than 39 [32]. This measurement will be collected at baseline and 6 weeks and 6 months postpartum.

Social support will be measured using the Multidimensional Scale of Perceived Social Support (MSPSS) [33]. This scale

provides a measurement of how much support a parent feels they receive from family, friends, and a significant other, and 3 subscale scores (with 4 items per subscale) can be calculated as well as a total score (from 12 to 84), with total scores indicating greater perceived support. If the total score and subscale scores are averaged over items, scores between 1 and 2.9 are considered "low support," 3 to 4.9 are considered "moderate support," and 5 to 7 are considered "high support" [34]. The MSPSS has been shown to be valid and internally reliable, with Cronbach α values ranging from .81 to .94 on individual subscales and from .83 to .92 for the total score [33].

Postpartum anxiety will be measured using the Postpartum Specific Anxiety Scale (PSAS) [35]. The PSAS is a valid and reliable instrument for assessing anxiety during the first 6 months postpartum, with Cronbach α values for individual factors ranging from .80 to .91, with an overall α value of .95 [35]. The optimal cutoff PSAS score for detecting clinical levels of anxiety is 112, with a sensitivity and specificity of 0.75 [35].

Postpartum depression will be measured using the 10-item Edinburgh Postnatal Depression Scale (EPDS) [36]. This scale can be used to screen mothers at risk for developing postpartum depression, with a score above 14 (out of 30) indicating a likelihood of having or developing postpartum depression [36]. The sensitivity of the EPDS was found to be 86% in women with depressive symptoms and 78% in women without depressive symptoms [36].

Implementation Outcomes

To measure the implementation extent of the Essential Coaching for Every Mother program, output data available through the Twilio and TextIt platforms [30,31] will be collected per participant including, but not limited to, enrollment rate, enrollment timing (postpartum or antenatal, days postpartum), number of withdrawals, and numbers of messages received. This data collection will continue throughout the trial and will be completed after the last follow-up contacts. To measure implementation quality, in the 6-week survey women in the intervention group will be asked about user experience, perspectives on the frequency and timing of messages, and what they liked and did not like about Essential Coaching for Every Mother. Using these measures, we seek to obtain data not only on implementation extent but also on the quality of the program through open-ended questions where mothers will be asked about their experience with Essential Coaching for Every Mother in practice.

Data Analysis

Data will be analyzed on an intention-to-treat basis (excluding women who requested to stop receiving the messages or were lost to follow-up). Demographic characteristics on maternal age, marital status, education level, and delivery method will be expressed as means and standard deviations or percentages, as applicable, based on group allocation. Postnatal contacts for themselves and their infants, health concerns, and feeding behavior will also be expressed as means and standard deviations or percentages, as applicable, based on group allocation. Any significant differences in baseline characteristics, examined through a chi-square analysis or Mann-Whitney test, will be adjusted for in the analysis. A *P* value of 0.05 will be considered significant for all outcomes.

For the primary outcome of self-efficacy, a total score will be reported using means, standard deviations, and percentages. Analysis of covariance (ANCOVA) will be used to measure whether total self-efficacy scores differ between the 2 groups, with adjustments for the pretest scores and any significant baseline characteristics.

For the first secondary objective, an ANCOVA will be used to determine whether scores differ between the 2 groups on social support, postpartum anxiety, and postpartum depression, with adjustments for the pretest scores and any significant baseline

characteristics. For the second secondary objective, a 2-way ANCOVA will be used to measure whether the mean difference of self-efficacy scores differs between the 4 groups (multiparous/primiparous and intervention/control), with adjustments for any significant covariates on self-efficacy, social support, postpartum anxiety, and postpartum depression. For the third secondary objective, a 2-way repeated-measures ANCOVA will be used to explore whether changes in the key psychosocial outcome variables varied over time.

For implementation data, summative data provided by the TextIt platform and Twilio interface will be reported, and descriptive statistics will be used to describe participants' experiences with Essential Coaching for Every Mother using means and standard deviations or percentages, as applicable. Open-ended questions from the survey will be analyzed using thematic analysis [37]. Greater understanding of the implementation extent indicators, in combination with the qualitative responses from mothers, will offer insight into the "black box" of the intervention to explore reasons for success or failure [38].

Results

Study recruitment started on January 5, 2021, and is currently ongoing, with an anticipated date of recruitment completion of January 2022.

Discussion

Given the lack of standardized postpartum education and support currently available, Essential Coaching for Every Mother is proposed to be an innovative solution to bridge this gap without adding a significant burden to the health care system. The goal of mHealth interventions in postnatal education is not to replace the need for in-person follow-up contacts, as these are important for health assessments of the woman and her infant by a skilled health care provider. Instead, mHealth interventions can be used to complement existing postnatal care by providing timely, standardized, relevant, and evidence-based information directly to women.

It is important to use a hybrid effectiveness-implementation design to evaluate both the Essential Coaching for Every Mother program and the process evaluation implementation to be able to offer suggestions for real-world implementation. This is the first postpartum text message program designed for women in Canada. It is expected that the findings will offer insights into whether the use of mobile technologies could be an effective strategy to ensure that research findings are effectively communicated to mothers to enhance postnatal experiences and care delivery in Nova Scotia. This strategy will also help to support the longevity of the research and may be easily transferable to other health centers and hospitals in Canada.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-review report.

[[PDF File \(Adobe PDF File\), 196 KB - resprot_v10i3e27138_app1.pdf](#)]

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Abbreviations

ANCOVA: analysis of covariance

CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile HEalth Applications and onLine TeleHealth

EPDS: Edinburgh Postnatal Depression Scale

KPCS: Karitane Parenting Confidence Scale

mHealth: mobile health

MSPSS: Multidimensional Scale of Perceived Social Support

PSAS: Postpartum Specific Anxiety Scale

REDCap: Research Electronic Data Capture

TIDieR: Template for Intervention Description and Replication

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Protocol

Telehealth Transition Assistance Program for Acute Spinal Cord Injury Caregivers: Protocol for a Mixed-Methods, Randomized Controlled Trial

Paul B Perrin^{1,2}, PhD; Scott D McDonald^{1,2}, PhD; Jack D Watson^{1,2}, BA; Bradford S Pierce^{1,2}, MS; Timothy R Elliott³, PhD

¹Virginia Commonwealth University, Richmond, VA, United States

²Central Virginia VA Health Care System, Richmond, VA, United States

³Texas A&M University, College Station, TX, United States

Corresponding Author:

Paul B Perrin, PhD

Virginia Commonwealth University

Box 842018

Richmond, VA, 23284

United States

Phone: 1 804 827 3894

Email: pperrin@vcu.edu

Abstract

Background: While spinal cord injury (SCI) caregiving can be a rewarding experience, caregivers often experience reduced mental and physical health.

Objective: This article describes the methodology of a study examining the efficacy of a newly developed telehealth Transition Assistance Program (TAP) for caregivers of individuals with acute SCI.

Methods: A mixed-methods, randomized controlled trial is comparing TAP outcomes to that of a standard-of-care control. The study is recruiting for 48 months and incorporating quantitative outcome measures.

Results: This study was funded by the Craig H. Neilsen Foundation in April 2017. It was approved by the institutional review boards at Virginia Commonwealth University and the Hunter Holmes McGuire Veterans Affairs Medical Center that same year. Participant recruitment and data collection began in 2018.

Conclusions: This study is implementing and testing an SCI caregiver intervention unlike any created before, targeting a critical time period that, until now, other SCI caregiver interventions have overlooked. Research personnel intend to disseminate the intervention and study findings through the publication of manuscripts and presentations at conferences. If the current study shows improvements in caregiver or patient well-being, the TAP for SCI caregivers could become part of the standard of care for acute SCI.

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KEYWORDS

spinal cord injury; telehealth; caregiver; methodology

Introduction

Each year in the United States, 18,000 individuals experience a new spinal cord injury (SCI), and nearly 294,000 are living with SCI [1]. Individuals with SCI experience myriad medical complications [2] and reduced mental health [3,4], which bears on their own health-related quality of life (HRQoL) [5].

Although only one family member typically experiences an SCI, the injury affects the entire family [2,6]. Many family caregivers experience strain, depression, anxiety, lower general health [7,8], and burden [9-11].

Unfortunately, SCI caregivers perceive inadequate support from their social network, profound isolation, and insecurity in the weeks after hospital discharge [12,13]. The first few months

are particularly stressful as caregivers cope with unstable social support and even their own wavering health [14]. Substantial research has been conducted on caregivers of individuals with various disabilities [15], but considerably less has focused on SCI caregivers. The current review uncovered several SCI caregiver interventions with empirical support; however, studies either did not target the specific acute discharge time period in the current study or psychosocial outcomes. Rodgers et al [16] developed the SCI Multiple-Family Group Treatment and targeted families who had been coping with SCI for 6 years on average. Schulz et al [11] compared the effectiveness of a caregiver-only intervention against an intervention for SCI caregiver-recipient dyads, but the individuals with SCI had sustained the SCI on average 7.7-9 years prior. Kurylo et al [17] developed the FOCUS program, which was incorporated by Elliott and Berry [18] into a formalized Problem-Solving Training program; however, no caregiver in either study participated during the first month after discharge. Molazem et al [19] showed positive results for a psychoeducational intervention on SCI caregiver HRQoL; however, the average length of time as a caregiver was 9 years. Hearn et al [20] showed that a web-based mindfulness intervention was helpful in reducing SCI caregiver anxiety and depression; however, the minimum length of time since injury was 1 year. Finally, Juguera Rodríguez et al [21] showed that simulation training for SCI caregivers during inpatient rehabilitation can improve competency in caregiver-related tasks but did not target psychosocial outcomes.

To improve SCI rehabilitation through stronger informal caregiving, this study is developing and evaluating a telehealth Transition Assistance Program (TAP) for caregivers of individuals with SCI during the transition from acute rehabilitation to home. This is the first SCI caregiver intervention to occur during this critical time and to target a host of important caregiving psychosocial variables. The TAP was previously developed for stroke caregivers [22] and is being modified for SCI and implemented at 2 state-of-the-art SCI rehabilitation facilities.

Methods

Study Design

This study is a prospective, mixed-method, randomized controlled trial incorporating a before-and-after design with a standard-of-care control wherein caregivers receive no formalized, structured postdischarge support. The study is recruiting over a period of 48 months.

Setting

The TAP program is delivered via telehealth at a Veterans Affairs (VA) medical center and an academic medical center in the same urban area.

Caregiver Guidebook Development

The research team developed a guidebook entitled “A Guidebook for SCI Caregivers” based heavily on research examining the needs of SCI caregivers, as well as on other published studies on SCI. Research has shown that the top reported needs of SCI caregivers include information, economic

support, emotional support, community support, and respite needs [23]. This guidebook was created to target these needs directly and therefore includes chapters addressing (1) basic medical information about SCI; (2) common caregiver experiences; (3) SCI recovery issues such as disability, disruption in sense of self, social isolation, and depression; and (4) resources to assist SCI caregivers. An extensive formative evaluation of the guidebook was conducted including focus groups with SCI clinicians at the rehabilitation facilities at the VA and academic medical centers. The guidebook was piloted with SCI clinicians and caregivers who provided quantitative and qualitative feedback on the guidebook’s appropriateness.

Participants, Recruitment, and Sample Size

The eligibility criteria for individuals with SCI and caregivers are the following: (1) between the ages of 18 and 89 years; (2) able to verbally communicate in English; (3) access to a computer, telephone, or other device capable of telecommunication; (4) no other serious mental or neurological disorders; (5) no active serious substance use disorder; and (6) being a dyad composed of 1 individual with a new diagnosis of SCI or significant new loss of function related to an old SCI and 1 individual identifying as a new informal caregiver. All individuals with SCI are those participating in a comprehensive residential rehabilitation program.

A power analysis was performed using G*Power 3.1. An estimated medium effect size of Cohen $f=.25$ was used to determine the sample size needed for a repeated-measures multivariate analysis of variance (RMANOVA) with 3 time points and 2 groups. With 80% power ($1 - \beta$), a sample size of 44 dyads is needed in order to detect the hypothesized medium-sized effects on the various outcomes. We selected a 48-month enrollment period because, based on SCI admissions data and previous studies conducted at the 2 rehabilitation sites, this window is necessary to enroll 44 patient-caregiver dyads ($n=88$), of which 22 dyads will be in the treatment group and 22 will be in the control group. This RMANOVA would uncover all large and medium-sized effects, but no small-sized effects.

Recruitment is conducted on site and in-person by either the research coordinator or the site’s principal investigator (PI). Patient-caregiver dyads are randomly assigned to the TAP treatment or control group, and each individual with SCI and caregiver is paid US \$20 per data collection for a total of US \$60 each.

Randomization

A randomization schedule was created with a web-based, computerized random number generator. We maintain allocation concealment and eliminate possible selection or recruitment biases by keeping the randomization schedule concealed from on-site staff engaged in recruiting. A randomization schedule was generated by the PI who does not have any contact with participants, and a sealed envelope with the sequentially numbered randomization schedule was prepared prior to recruitment of any participants. After a project coordinator determines eligibility for a prospective dyad and obtains informed consent, the PI is notified and then opens the sealed envelope. The group assignment based on the predetermined

sequence for that participant to 1 of the 2 groups is revealed at that point. If the participant is in the TAP group, an interventionist is then assigned to that participant. In order to control bias and preconceptions in collecting data, the interventionist does not collect baseline or follow-up data from participants with whom they intervene.

Intervention Implementation

The TAP is carried out by a psychology PhD student interventionist who underwent rigorous training. The interventionist is responsible for scheduling and following up with caregivers under his or her care, and the same interventionist administers all sessions for a single caregiver in order to maintain consistency across sessions, unless extenuating circumstances arise. To ensure TAP intervention fidelity, the PI reviews the interventionists' recordings for the first full 5 sessions that the interventionist conducts. A checklist was developed that covers the content specific to each session and an assessment of the interventionist's interaction with the caregiver. The PI provides a summary of strengths, shortcomings, and recommendations for improvement so that any errors can be corrected immediately and not be repeated.

Intervention

Session 1

The PI and collaborators trained a psychology PhD student to serve as an interventionist and provide the TAP. In preparation for Session 1 with the caregiver, the interventionist delivering the TAP meets with the facility's rehabilitation team (and in particular, the SCI interdisciplinary team collaborators and consultants on the grant) to identify the primary difficulties anticipated for the individual with SCI after discharge. The interventionist takes notes on the particular needs and bring these notes to Session 1 with the caregiver. Before discharge, the interventionist implements Session 1, a 1-hour meeting with each caregiver in the intervention group only. The primary focus of Session 1 is to orient the caregiver to the TAP and prepare the caregiver for discharge home. The interventionist provides the caregiver the guidebook and orientation to it, encouraging the caregiver to use it as a resource (caregivers in the control group receive a copy of the caregiving guidebook after the final data collection). The interventionist asks what concerns the caregiver has caring for the individual with SCI after discharge, taking notes on the caregiver's responses. The interventionist shares with the caregiver the difficulties that the rehabilitation team had anticipated the individual with SCI will experience after discharge. The interventionist provides support and helps the caregiver problem solve caregiving related to these issues.

Sessions 2-5

The interventionist administers four 1-hour telehealth clinic-to-home sessions with the SCI caregiver at 1, 2, 4, and 6

weeks after hospital discharge. One of the rehabilitation centers already had in place secure and encrypted telehealth technology that allows an interventionist on-site to meet virtually with a caregiver at home via personal computers or mobile devices. For caregivers who do not have a personal computer, mobile device, or adequate internet connection, a telephone-based approach is used. The individual with SCI may or may not be in the same room as the caregiver during these sessions, depending on the wishes of the caregiver. These sessions involve the same general format. The interventionist brings his or her notes from the previous sessions and from the rehabilitation team's input. The interventionist reviews the content of these notes with the caregiver, checking in to see whether the problems are still present and to what extent. The interventionist engages in supportive problem solving and refers the caregiver to the guidebook sections relevant to the issues, walking the caregiver through those sections. Because of this format, the TAP is specifically designed for interventionists to tailor its use in future studies or administrations not only according to possible facility differences in what may be necessary for the intervention but also for differences in caregiver responsibilities and needs within a single facility. The entire structure of the TAP is centered around the caregiver's most pressing needs. The interventionist takes notes on the continued problems and strategies for resolving them.

Data Collection

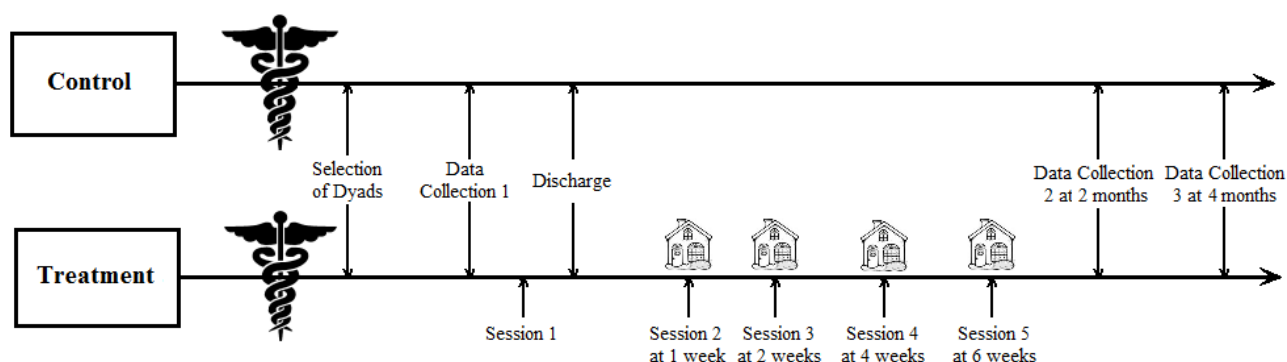
Data Collection 1

After enrollment and immediately before discharge (as well as before Session 1 for the TAP group), demographic and baseline data are collected from the individual with SCI and caregiver separately by a study coordinator. A study coordinator reads items aloud from an assessment packet (unless a participant explicitly requests a paper-and-pencil format) to the individual with SCI and caregiver, noting participants' responses. The caregiver packet includes validated measures of caregivers' quality of informal care provided, depression, relationship satisfaction, burden, caregiving self-efficacy, health status, and positive affect/well-being. The packet for the individual with SCI includes validated measures of functional status, perceptions of quality of informal care received, depression, relationship satisfaction, self-perceived burden, health status, and positive affect/well-being. In rare cases, after Data Collection 1 has been conducted, where the patient's discharge is moved to a later date, data collection may be readministered to ensure data accuracy.

Data Collection 2-3

At 2 and 4 months, a study coordinator collects follow-up data from the individual with SCI and caregiver over the phone using the same validated measures as during the first data collection. A graphic depicting the study timeline can be seen in [Figure 1](#).

Figure 1. Randomized controlled trial timeline.



Outcome Measures

Exemplary Care Scale

The Exemplary Care Scale is administered for both patient and caregiver and is an 11-item self-report questionnaire that assesses the extent to which caregivers engage or do not engage in activities that help care recipients maintain dignity and respect [24]. Parallel caregiver and care recipient versions are available with equivalent measurement properties.

Spinal Cord Independence Measure Version III

The Spinal Cord Independence Measure Version III is completed by the patient and is a 19-item self-report questionnaire that assesses functioning of individuals with SCI in 3 domains: self-care, respiration and sphincter management, and mobility. Higher scores indicate greater patient functioning [25].

Center for Epidemiologic Studies Depression Scale-Revised

The Center for Epidemiologic Studies Depression Scale-Revised (CESD-R) is completed for both the patient and caregiver. The 20-item CESD-R [26] is the revised version of the original CESD [27], and higher total scores reflect higher depression symptomology.

Self-Perceived Burden Scale

The Self-Perceived Burden Scale is completed by the patient and assesses care recipients' feelings of dependence and guilt regarding their caregiver's difficulties [28]. The Self-Perceived Burden Scale contains 10 items, and higher scores indicate higher self-perception of being a burden.

Zarit Burden Interview

The Zarit Burden Interview [29] is completed by the caregiver and is a 22-item, self-report measure of caregiver burden with items referring to the caregiver and patient relationship and evaluating the caregiver's health condition, psychological well-being, finances, and social life. Higher total scores indicate greater burden.

Revised Scale for Caregiving Self-Efficacy

The Revised Scale for Caregiving Self-Efficacy [30] is completed by the caregiver and measures 3 domains of caregiving self-efficacy: obtaining respite, responding to disruptive patient behaviors, and controlling upsetting thoughts.

12-Item Short Form

Both the patient and caregiver complete the 12-item Short Form (SF-12). The SF-12 is one of the most widely used assessments of HRQoL in individuals with neurological conditions and their caregivers [31]. The SF-12 has 8 dimensions: physical function, role-physical, bodily pain, general health, energy/vitality, social function, role-emotional, and mental health. Higher scores indicate better HRQoL.

SCI-QOL Positive Affect and Well-Being Short Form

The Positive Affect and Well-Being Short Form [32] is completed by both the patient and caregiver and is a 10-item version of the National Institutes of Health Patient-Reported Outcomes Measurement Information System that has been tailored and optimized for the SCI population. Higher scores reflect greater positive affect and well-being.

Data Analysis

A Greenhouse-Geisser-adjusted RMANOVA with 1 fixed effect of treatment condition (TAP vs control), the repeated measures over time (baseline and 2 and 4 months after discharge), and the treatment condition by time interaction will be conducted for the set of dependent variables. If an omnibus effect is found, follow-up Holm-Bonferroni-corrected ANOVAs will identify specific locations of effects. Our research has shown that these dependent variables rarely correlate with each other higher than .60 in SCI caregivers [5] so do not reach the .70 level that is often identified as problematic in RMANOVA [33].

Results

This study was funded by the Craig H. Neilsen Foundation in April 2017 (Multimedia Appendix 1). It was approved by the institutional review boards at Virginia Commonwealth University and the Hunter Holmes McGuire Veterans Affairs Medical Center that same year. Participant recruitment and data collection began in 2018. As of March 2021, 31 caregiver-patient dyads (n=62) had enrolled in the study. Data analysis will begin toward the end of the grant cycle in March 2022, with results expected to be published in May 2022.

Discussion

One primary goal of this study is to actively affect the care of individuals with SCI and their informal caregivers at a systematic level. As such, the caregiver guidebook developed

for this study will be made freely available online so that any clinician may give it to any new, informal caregivers as they adjust to their new role. If the results are significant, the research team will make the intervention and results available through manuscripts and conference presentations. Detailed descriptions of the intervention will be published, and training videos will be made available online.

This study's use of PhD psychology students as the study's interventionists allows for a role that could create a future pipeline and documentation for training rehabilitation psychology students using the TAP system. Students could also receive course credit for practicum work in SCI rehabilitation settings while simultaneously gaining experience in telepsychology and with underserved populations. The use of PhD psychology students as interventionists helps defray health care costs and reduces the burden placed on the medical center's staff [34].

The TAP intervention, especially if used as a training program for PhD students, could be implemented for minimal or even negligible health care costs. These savings could be passed to the individual with SCI and his or her informal caregiver. We

also anticipate that participants will find the telepsychology intervention to be both more convenient and less of a strain on their resources than traditional, in-person sessions.

Given the study's presence at both a VA medical center and an urban academic medical center, any study findings should have high generalizability to both the general population and veterans with SCI. Our TAP for SCI caregivers is innovative in that it fills one of the biggest gaps in SCI rehabilitation by aiming to improve the mental health of and quality of informal care provided by caregivers immediately as they transition into their caregiving role. The study's telehealth format surmounts geographical barriers and links SCI caregivers via telehealth technology to the specialized center from which the individual with SCI received acute rehabilitation, thereby overcoming the discontinuity in care that all too often affects individuals with SCI and their family after discharge. If shown in the proposed study to improve caregiver mental health, informal care, and SCI rehabilitation, the TAP for SCI caregivers could be exported and evaluated much more widely across other rehabilitation facilities in the United States and hopefully become part of the standard of care for SCI.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-review report by Craig H Neilsen Foundation.

[PDF File (Adobe PDF File), 152 KB - [resprot_v10i3e28256_app1.pdf](#)]

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Abbreviations

CESD-R: Center for Epidemiologic Studies Depression Scale-Revised

HRQoL: health-related quality of life

PI: principal investigator

RMANOVA: repeated-measures multivariate analysis of variance

SCI: spinal cord injury

SF-12: 12-item Short Form

TAP: Transition Assistance Program

VA: Veterans Affairs

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Protocol

Effect of Reading Rehabilitation for Age-Related Macular Degeneration on Cognitive Functioning: Protocol for a Nonrandomized Pre-Post Intervention Study

Walter Wittich^{1,2,3,4,5,6}, PhD, CLVT, FAAO; M Kathleen Pichora-Fuller⁷, PhD; Aaron Johnson^{3,4,5}, PhD; Sven Joubert^{8,9}, PhD; Eva Kehayia^{4,6}, PhD; Vanessa Bachir^{1,4}, MSc, OD; Gabrielle Aubin^{2,3,4,8}, BSc; Atul Jaiswal^{1,2,4}, PhD; Natalie Phillips⁵, PhD

¹School of Optometry, Université de Montréal, Montreal, QC, Canada

²Institut Nazareth et Louis-Braille du CISSS de la Montérégie-Centre, Longueuil, QC, Canada

³Centre de réadaptation Lethbridge-Layton-Mackay du CIUSSS du Centre-Ouest-de-l'Île-de-Montréal, Montreal, QC, Canada

⁴Center for Interdisciplinary Rehabilitation Research of Greater Montreal, Montreal, QC, Canada

⁵Department of Psychology, Concordia University, Montreal, QC, Canada

⁶School of Physical and Occupational Therapy, McGill University, Montreal, QC, Canada

⁷Department of Psychology, University of Toronto at Mississauga, Mississauga, ON, Canada

⁸Department of Psychology, Université de Montréal, Montreal, QC, Canada

⁹Centre de recherche de l'Institut universitaire de gériatrie de Montréal, Montreal, QC, Canada

Corresponding Author:

Walter Wittich, PhD, CLVT, FAAO

School of Optometry

Université de Montréal

3744, rue Jean-Brillant

room 260-7

Montreal, QC, H3T 1P1

Canada

Phone: 1 514 343 7962

Fax: 1 514 343 2382

Email: walter.wittich@umontreal.ca

Abstract

Background: Age-related vision impairments and dementia both become more prevalent with increasing age. Research into the mechanisms of these conditions has proposed that some of their causes (eg, macular degeneration/glaucoma and Alzheimer's disease) could be symptoms of an underlying common cause. Research into sensory-cognitive aging has provided data that sensory decline may be linked to the progression of dementia through reduced sensory stimulation. While hearing loss rehabilitation may have a beneficial effect on cognitive functioning, there are no data available on whether low vision rehabilitation, specifically for reading, could have a beneficial effect on cognitive health.

Objective: The research questions are: (1) Does low vision rehabilitation reduce reading effort? (2) If so, does reduced reading effort increase reading activity, and (3) If so, does increased reading activity improve cognitive functioning? The primary objective is to evaluate cognition before, as well as at 6 months and 12 months after, 3 weeks of low vision reading rehabilitation using magnification in individuals with age-related macular degeneration, with or without coexisting hearing impairments. We hypothesize that improvements postrehab will be observed at 6 months and maintained at 12 months for participants with vision loss and less so for those with dual sensory loss. The secondary objective is to correlate participant characteristics with all cognitive outcomes to identify which may play an important role in reading rehabilitation.

Methods: We employ a quasiexperimental approach (nonrandomized, pre-post intervention study). A 3x3 design (3 groups x 3 time points) allows us to examine whether cognitive performance will change before and after 6 months and 12 months of a low vision reading intervention, when comparing 75 low vision and 75 dual sensory impaired (vision & hearing) participants to 75 age-matched healthy controls. The study includes outcome measures of vision (eg, reading acuity and speed), cognition (eg,

short-term and long-term memory, processing speed), participant descriptors, demographics, and clinical data (eg, speech perception in noise, mental health).

Results: The study has received approval, and recruitment began on April 24, 2019. As of March 4, 2021, 38 low vision and 7 control participants have been enrolled. Lockdown forced a pause in recruitment, which will recommence once the COVID-19 crisis has reached a point where face-to-face data collection with older adults becomes feasible again.

Conclusions: Evidence of protective effects caused by reading rehabilitation will have a considerable impact on the vision rehabilitation community and their clients as well as all professionals involved in the care of older adults with or without dementia. If we demonstrate that reading rehabilitation has a beneficial effect on cognition, the demand for rehabilitation services will increase, potentially preventing cognitive decline across groups of older adults at risk of developing macular degeneration.

Trial Registration: ClinicalTrials.gov NCT04276610; Unique Protocol ID: CRIR-1284-1217; <https://clinicaltrials.gov/ct2/show/NCT04276610>

International Registered Report Identifier (IRRID): DERR1-10.2196/19931

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KEYWORDS

low vision; rehabilitation; cognition; aging; dementia; reading

Introduction

Sensory and Cognitive Loss—An International, National, and Local Priority

Prevention and treatment of cognitive impairments in the aging population have become priorities for stakeholders in health care research around the globe. In Canada, the Senate Report on the need for a Canadian Dementia Strategy was released in 2017 [1], and resulting recommendations started to be made public in 2019 [2]. For example, the importance of vision and hearing is mentioned in order to promote and enable early diagnosis, with the goals of increasing quality of life and improving social connectedness, belonging, and purpose. These initiatives specifically refer to the importance of vision and hearing health research. Internationally, recent publications in *The Lancet* [3,4] described dementia as the most challenging threat to population health in our century and pointed out that hearing loss may be the largest potentially modifiable risk factor for cognitive impairments. While low vision rehabilitation (eg, magnification strategies and reading rehabilitation) may serve as a potential prevention strategy for cognitive decline, this possibility is notably absent from this review. There is simply a lack of evidence from longitudinal or intervention studies regarding the links between visual loss and cognitive impairments [5]. Some researchers have indicated that improvement of vision through cataract surgery has resulted in improved scores on attention, orientation, memory, language, visual perceptual, and visuospatial skills as measured by the Addenbrooke's Cognitive Examination or the Revised Hasegawa's dementia scale [6,7]; however, improvements in global scores across these cognitive domains did not replicate when using the Telephone Interview of Cognitive Status [8,9]. This may in part be explained by the fact that some of these researchers chose to utilize cognitive measures [10] that contain items that require vision without any adaptations to confirm the visibility of these test items. Others utilized nonvisual measures of cognition [11,12], thereby avoiding the possible influence of improved vision masking as improved cognition on visual test items. Apart from medical interventions such as cataract

surgery, the main technique to improve visual input for reading in the presence of low vision has been magnification; however, vision rehabilitation has never been systematically evaluated using cognitive outcome measures.

Comorbidity of Ocular Disease and Cognitive Impairments

There is a growing body of evidence linking age-related eye diseases such as age-related macular degeneration (AMD) with changes in cognitive functioning and cognitive impairments due to Alzheimer's disease (AD) [13-17]. The prevalences of AMD and AD increase with increasing age [18-21]; both conditions share many risk factors (eg, smoking, obesity, age, and unhealthy diet [22]), yet their comorbidity is higher than what would be expected if they were independent of each other [23-25]. The anatomical changes observed in both AMD (eg, drusen development in the retina) and AD (eg, formation of plaques in the brain) are possible symptoms of a common underlying disease mechanism within the central nervous system. Specifically, the buildup of beta amyloid found in plaques and drusen could indicate a common pathogenesis for both diseases [26-28]. Furthermore, declines in visual and cognitive functioning are correlated [29-31]; for example, higher cognitive function scores on the Mini-Mental State Examination (MMSE) were associated with better best-corrected visual acuity [29], when the visual items on this cognitive screening test are either included or excluded [31]. Declining scores on a modified and expanded version of the MMSE correlated with declines in visual acuity, contrast sensitivity, and stereo acuity impairments over 9 years in a population-based study of community-dwelling, highly physically functioning older adults [30]. It is less clear, however, whether these declines can be modified with vision interventions, given that the MMSE is a screening tool covering multiple aspects of cognition but none at great depth. There is some evidence that individuals who read frequently are at reduced risk of developing cognitive impairments [32]. In addition, it is not surprising that there is overlap between the behavioral aspects of AMD and AD; for example, social disengagement and functional impairments in

activities of daily living may be present as a result of either or both conditions.

Low Vision Makes Reading More Effortful

The Framework for Understanding Effortful Listening has been used to illustrate how listeners with a hearing impairment allocate more cognitive resources in challenging conditions (such as when an individual has hearing loss or there is noise) [33]. Similarly, reading becomes more effortful in the presence of central visual impairment or when visual input is suboptimal. For example, AMD generally causes a reduction in visual acuity, making it necessary for persons living with AMD to utilize magnification in order to read with peripheral retina that is still intact [34,35]. Given that fixation in the periphery is less stable [36], more concentration and effort are required to read magnified text with a peripheral retinal locus [37,38]. Effortful viewing or reading explains why the presence of central visual impairment (eg, the presence of central scotoma and resulting drop in visual acuity) has repeatedly been correlated with reduced reading speed as low as 20-40 words per minute [39], whereby poorer fixation stability has been associated with slower reading speeds [40]. Increased cognitive load leads to a decrease in the attentional visual window [41]. As individuals with vision loss find reading more effortful, thus experiencing a higher cognitive load, their attentional window should shrink. Processing of visual information in the retinal periphery (as is necessary in persons living with AMD) is slower and not as efficient as in the macular region [42], in both younger and older observers [43]. In addition, low vision affects eye movements during reading, thereby further shrinking the perceptual window where letters are processed, likely due to the increase in cognitive demand [44]. Importantly, when some cognitive resources are diverted to this reading effort, remaining cognitive resources may be insufficient for readers to rapidly or accurately process (comprehend or remember) the information that was seen or read.

Low Vision Rehabilitation Reduces Reading Effort

Difficulty while reading is the most common functional complaint in persons with low vision, and improving the ability to read is often the main purpose of vision rehabilitation interventions [45]. The effectiveness of low vision rehabilitation has been demonstrated repeatedly [46,47], specifically for reading [48]. A systematic review confirmed that there is strong evidence that low vision reading rehabilitation services improve reading ability overall [49]. Both magnification devices (eg, handheld magnifiers, closed-circuit televisions, or zoom functions on an iPad [50,51]) and large print appear to be equally effective [52]. Increasing reading performance (eg, increasing reading speed at decreased print size or improving comprehension) is frequently the main target for improvement during rehabilitation [49,53]. It has been used as the primary outcome measure in recent clinical trials demonstrating the effectiveness of low vision treatments [49,53]. Individuals living with low vision can be trained to use either closed-circuit television video magnifiers or mechanical magnification devices (eg, handheld magnifiers, telescopes) to help improve reading performance by up to 200% [54]. One central underlying goal of low vision rehabilitation is to reduce the effort that is required

to accomplish visual tasks in the presence of a visual impairment [55]. Measuring this effort (or its reduction) can be done subjectively by asking participants whether they perceive less effort during completion of the task. However, there are also a variety of observable variables that can be used as indicators of reduced reading effort. They include improved reading speed (eg, reading becomes faster as it becomes easier) and improved reading comprehension (eg, less effort liberates cognitive resources for processing and retention [33]). Interestingly, the findings for reading comprehension in the presence of low vision are mixed [56] insofar as reading speed (as an indicator of effort), scotoma size, and visual acuity all influence comprehension. However, most studies on low vision reading have small sample sizes and are underpowered. Therefore, it is hard to control for factors such as scotoma size or acuity impairment, a problem we hope to overcome in our study by recruiting a larger number of participants than is generally the case in studies on low vision and reading.

The Link Between Reading and Cognition

Reading is a complex process that involves bottom-up visual processing to enable grapheme (ie, letter) recognition that in turn enables grapheme-to-phoneme conversion, leading to word recognition and the identification of morphosemantic, syntactic, and pragmatic features of lexical items that are ultimately used in the comprehension of sentences and discourse such as stories [57]. Because reading is subserved by a number of cognitive processes, including attention, long-term memory, and working memory, there is a symbiotic relationship between reading and cognitive processing as has been documented extensively in the psycholinguistic/neurolinguistic and brain imaging literature [58,59]. Notably, a number of studies has shown that engaging in high-level cognitive activities, such as reading text, appears to preserve cognition in aging adults. The frequency of participation in activities that are mentally stimulating, such as reading, is associated with lower risk of incident AD [59-61]. Researchers have also linked reading and engaging in higher-level cognitive activities with increased cognitive reserve, that in turn is associated with more tolerance of AD pathology and stimulation of brain plasticity [62-65].

Does Reduced Reading Effort Lead to Improved Cognition?

We previously found a positive correlation between reading speed and higher scores on the Montreal Cognitive Assessment (MoCA) in persons with AMD [66,67]. Given the information reviewed in the previous sections, the logical direction for our investigation into the functional connection between low vision and cognition is to examine the possible effects of reading rehabilitation on the cognitive abilities of individuals undergoing low vision rehabilitation. In order to disentangle the effects of visual and cognitive impairments in older adults, members of this research team have adapted cognitive tests so they can be administered to individuals with low vision [68,69]. In parallel, we are also in the process of developing a vision-screening test that can be administered to individuals with various levels of cognitive impairment [70,71]. This investigation will guide our future research efforts into the improvement of service provision in low vision rehabilitation for the purpose of increasing the

independence and cognitive health of older adults living with low vision.

Objectives and Hypotheses

The overall goal of the study is to demonstrate that low vision rehabilitation will improve reading, which, in turn, will improve cognition.

The primary objective is to measure global changes in reading ability and cognitive functioning before and after 6 months and 12 months of reading rehabilitation. Hypothesis 1 is that improvements relative to pretreatment performance will be observed at 6 months and maintained at 12 months for participants with vision loss only and less so for those with dual sensory impairment (DSI). Control participants are expected to have stable performance and outperform both groups who receive reading rehabilitation. The global reading outcomes are reading speed, reading comprehension, and subjective perception of reading effort.

The global measure of cognition is the MoCA.

The secondary objective is to explore changes in more specific subdomains of reading ability and cognitive functioning. Hypothesis 2 is that improvements relative to pretreatment performance will be observed at 6 months and maintained at 12 months for participants with vision loss only and less so for those with DSI. Control participants are expected to have stable performance and outperform both groups who receive reading rehabilitation. The specific reading outcomes are reading acuity, critical print size, reading accuracy, and subjective reports of changes in reading habits.

The specific measures of cognition are episodic learning; memory encoding, storage, and retrieval; attention, speed, and mental flexibility; and semantic fluency.

Hypothesis 3 is that improved reading behavior will be correlated with improved cognitive functioning across all 3

groups, with the strongest relationship being in the AMD-only group. Such correlations will be observed across the global as well as the specific measures.

The tertiary objective is to explore factors that may influence the cognitive benefits of reading rehabilitation. Hypothesis 4 is that individual differences in the association between improved reading behavior and cognitive functioning may be related to participant characteristics such as demographic variables, hearing impairment severity, and mental health.

Study Design

We present this protocol following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [72]. An overview of the trial registration data is provided in Table 1. We decided on a 3-arm, quasiexperimental, repeated-measures design (nonrandomized, pre-post intervention study) [73], whereby participants act as their own comparison across time points. Given the prevalence of hearing loss among older adults, we decided to include both patients with AMD who present with normal hearing [74,75] and those who experience both vision and hearing loss (DSI). We decided to add an age-matched control group with healthy vision and hearing in order to observe the size of possible practice effects and record general variability in the measures, given the expected advanced age of our participants. The rehabilitation center partners on this study generally provide reading rehabilitation within 3 months of the initial optometric assessment. Therefore, we chose 6 and 12 months as suitable follow-up time points. After 6 months, the initial interventions will be completed, and participants will have had 3 months to engage in reading postintervention. Overall, a design with 3 groups (AMD-only, DSI, comparison) x 3 test times (preintervention, 6 months, 12 months) is planned to allow us to examine whether cognitive performance will change over time and if the degree of change and the final performance on outcome measures will differ across groups.

Table 1. Trial registration data.

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov ID: NCT04276610
Date of registration in primary registry	February 19, 2020
Secondary identifying numbers	CRIR-1284-1217
Source(s) of monetary or material support Primary sponsor	Fonds de recherche Quebec - Santé & Turmel Foundation (years 1 & 2); Canadian Institutes of Health Research Project Grant: Patient-Oriented Research Priority Announcement (year 3)
Contact for public queries	Walter.wittich@umontreal.ca
Contact for scientific queries	Walter.wittich@umontreal.ca; natalie.phillips@concordia.ca
Public & scientific title	Words on the Brain: Can Reading Rehabilitation for Age-Related Vision Impairment Improve Cognitive Functioning?
Countries of recruitment	Canada
Health condition(s) or problem(s) studied	Age-related macular degeneration Dementia
Intervention(s)	Behavioral: Low Vision Reading Rehabilitation
Study type	Interventional clinical trial, nonrandomized, parallel assignment
Date of first enrollment	April 24, 2019
Target sample size	225
Recruitment status	Recruiting

Methods

Study Setting

The study will be conducted at 2 partnering vision rehabilitation centers in the Montreal area, the Centre de réadaptation Lethbridge-Layton-Mackay du Centre intégré universitaire de santé et de services sociaux du Centre-Ouest-de-l'Île-de-Montréal and the Institut Nazareth et Louis-Braille du Centre intégré de santé et de services sociaux de la Montérégie-Centre. Both sites are part of the Center for Interdisciplinary Rehabilitation Research of Greater Montreal and provide government-funded rehabilitation services, free of charge for eligible residents of Quebec, Canada.

Eligibility Criteria

Inclusion Criteria

Participants in the intervention groups (AMD-only and DSI) are required to have a primary diagnosis of AMD (any type, as drusen-containing beta amyloid are found in all types of AMD [26-28]) as confirmed by the ophthalmologist or optometrist who referred the individual to the vision rehabilitation centers. They must be able to benefit from a magnification intervention for the purpose of improving their ability to read, according to the clinical judgment of their rehabilitation professionals who coconstruct their personalized intervention plans. All participants need to be able to communicate in either English or French (their choice of dominant language) and have a distance visual acuity in the better eye of 20/60 or less with best standard refraction, according to the admission criteria for eligibility for rehabilitation services in Quebec [76]. Individuals in the healthy control group are required to have age-normal hearing and vision (visual acuity better than 20/40 in the better eye, no diagnosis

of visual impairment in the last 12 months) [77]. In line with the hearing impairment categorizations used in Quebec [78], participants with unaided pure-tone averages (PTAs) across .5, 1, 2, and 4 kHz in the better ear of 40 decibel hearing level (dB HL) or less will be considered to have no or mild hearing impairment. Those with PTAs between 41 and 79 dB HL will be considered participants with moderate to severe hearing impairment and will be allocated to the DSI group. We will also recruit 75 age-matched older adults without visual impairment.

Exclusion Criteria

Participants cannot currently be undergoing any medical treatment for their AMD (eg, antivasular endothelial growth factor therapy injections). They must have sufficient residual vision to benefit from magnification for the purpose of reading printed paragraphs (visual acuity in the better eye of 20/400 or better). Based on past experience with participant recruitment over the phone, recruitment success over the phone is low with individuals living with more severe degrees of hearing impairment. Therefore, those whose file information indicates an audiogram with an unaided PTA ≥ 80 dB HL in their better ear will not be approached for recruitment [79]. In order to facilitate the administration of informed written consent through the research assistants and to focus recruitment on older adults with the necessary cognitive capacities to complete a somewhat lengthy protocol, individuals whose file information indicates a diagnosis of an advanced cognitive impairment such as AD will not be approached for recruitment. Participants whose total score on the MoCA is below 18 or whose score on the blind MoCA is below 10 will not be included in the study, because our clinical and research experience [80] has indicated that individuals with scores at that level are likely too cognitively impaired to complete a research protocol with this level of

complexity. At the initial assessment, both the PTA and MoCA scores will be used to determine if participants continue further in the study.

Intervention

Rehabilitation services at the partner centers will deliver the low vision evaluation and reading rehabilitation intervention, as regulated by the Quebec Ministry of Health. Typically, within 3 months of their initial low vision rehabilitation assessment, individuals will receive most of the recommended interventions. The clinical staff and rehabilitation professionals at either rehabilitation center decide which components of the full complement of services are suited for each participant. The 2 centers offer comparable services, including the provision of assistive devices and services, as regulated by the Quebec Health Insurance Program. These services are similar to those provided within the Blind Rehab Centers of the Veterans Affairs service in the United States [46,47]. They include, but are not limited to, a full optometric exam to determine functional vision, including refraction and the prescription of appropriate near and distance glasses and optical devices; an assessment by a low vision therapist or occupational therapist to establish the participant's functional priorities and rehabilitation goals; and the provision of handheld optical magnification devices, electronic nonoptical magnification devices (eg, portable or tabletop closed-circuit TVs), or computer software for screen content magnification (eg, ZoomText). All devices are provided free of cost for the individual and with appropriate training and follow-up sessions at home within 3 months of the initial intervention, as required. The rehabilitation professionals may perform a systematic lighting assessment in the participants' homes [81-83] and may make specific lighting recommendations that are intended to improve their reading ability. In addition, participants will have access to referral services such as orientation and mobility training (for independent travel) or registration with an adapted adult day center for individuals with sensory loss [80]. These centers provide access to psychosocial services, counsellors, social workers, or other mental health professionals. The provision of assistive devices for magnification and reading is generally linked to a follow-up visit in the individual's home 3 weeks after the initial rehabilitation appointment. At this time, rehabilitation professionals observe the use of the devices and strategies in the environment where the participant lives. It is at this point that the professionals together with the participants decide whether the devices are useful and are assigned as a permanent loan. Should additional needs emerge, the participant is at liberty to contact the rehabilitation center at any time to initiate a new service episode. The rehabilitation professionals record all aspects of this intervention in the rehabilitation files, to which the research team will have access during and at the end of the 12-month study period.

Outcomes

Test Administration

The order of test administration begins with the primary (MoCA, Minnesota Low Vision Reading Test, International Reading Speed Test, reading habits questionnaire) followed by the secondary and then the participant characteristics measures;

should a participant be unable to complete any one of the measures due to its complexity or to fatigue, the experimenter moves on to the next test, using personal judgment as to the participant's level of fatigue. Participants are encouraged to take as many breaks as they desire in order to facilitate completion of the maximum number of tests possible. Incomplete tests will not be scored; however, the number of completed tests at each testing session will be compared. Note that cognitive test administration can be adjusted to make instructions audible for persons with hearing loss. Ambient lighting at home in the room where participants generally read and where the tests are administered will be measured using a Digital Illuminance Meter (model LX1330B, Dr. Meter, Union City, CA).

Cognition Outcome Measures

All cognitive measures are administered in the auditory domain and thus will not be affected by a visual impairment. Therefore, should performance on the cognitive measures improve following the vision rehabilitation program, the improvement should be attributable to the benefit of increased visual function on cognitive stimulation as opposed to merely being due to improved perception of the stimuli involved in the tests. It is reasonable to expect improvement on the chosen cognitive measures as a result of the reading intervention and within the timeframe of the study. Notably, the chosen measures assess cognitive domains that have been shown to predict everyday function in older adults: episodic learning and memory [84], processing speed [85], and working memory [86].

General cognition will be measured using the MoCA [87] or its adapted version for persons with visual impairment (MoCA-Blind [68]). Should participants be unable to complete the visual items of this test because their vision is too severely impaired, the adapted version will be administered. The measure covers aspects of executive functioning, memory, language, abstraction, and orientation in time and space. Scoring ranges from 0 to 30 (MoCA) or 0 to 22 (MoCA-Blind), with higher scores indicating better performance. A score of 26 on the MoCA or 18 on the MoCA-Blind is the cut-off indicating that an individual may be at risk for having mild cognitive impairments [68,87]. The MoCA has good psychometric properties (internal reliability: $\alpha=.83$; test-retest reliability: $r=.92$; validity: $r=.87$). The MoCA is available in multiple equivalent versions and in multiple languages. One of the 3 available versions of the MoCA will be assigned randomly for each participant at the first session in order to reduce practice effects. The other 2 versions will be used for sessions 2 and 3.

Auditory episodic learning and memory will be assessed using the Rey Auditory Verbal Learning Test (RAVLT) [88]. This test evaluates memory encoding, storage, and retrieval. Its psychometric properties indicate an internal reliability of .90 and test-retest variability ranging from $r=.60$ to $r=.70$ [88]. Both parts of the RAVLT (acquisition, as well as delayed recall and recognition) will be used. In the acquisition part of the test, the experimenter reads a list of 15 words that the participant needs to repeat immediately afterwards. The experimenter reads the list 5 times, and after each time, the participant repeats the words remembered from the same 15-word list. The experimenter then

reads a second list of words once in order to create interference. The participants are asked to say as many words as they can remember from this list. After the interference task, the participant is asked to recall as many words as possible from the first list. After a 20-minute break, the participant is asked to recall as many words as possible from the first list. Then, the experimenter reads a list of 50 words and asks the participant to identify which of these words were contained in the first list (recognition task). Acquisition (ie, number of words recalled in the first 5 trials), delayed recall (ie, the number of words recalled after the 20-minute interval), and recognition (ie, number of words correctly identified in a 50-word list) are the components of the RAVLT. Higher scores indicate better performance.

The Oral Trail Making Test parts A & B [89] evaluate sequential set-shifting without the motor and visual demands of its written counterpart, thereby being ideally adapted for persons with visual impairment [88]. This test assesses attention, speed, and mental flexibility. Validity has been reported at .68 for Part A and .72 for Part B [88]. In part A of the test, participants are asked to count from 1 to 25 as fast as possible while maintaining intelligibility. In part B, they are asked to count to 13 by alternating a number and a letter in numerical and alphabetical order. The outcome measure is the time, in seconds, participants take to complete the task, with lower scores indicating better performance.

Semantic fluency describes the ability to successfully retrieve specific information within a time limit. Fluency will be measured with the letters F, A, and S, as well as by animal naming [90]. Reported psychometric properties include internal reliability of $r=.83$, test-retest reliability of $r=.74$, and validity ranging from $r=.85$ to $r=.94$ [88]. Specifically, the participant is asked to generate as many words as possible starting with the letters F, A, and S, as well as to name as many animals as possible, all within 1 minute. The instructions are to avoid repetitions, proper names, or slang. Higher scores indicate better performance.

Reading Outcome Measures

The secondary measures pertain to reading, including past and present reading habits, reading acuity, reading speed, and reading comprehension. These measures will demonstrate if there are direct benefits from low vision rehabilitation on reading. Multiple tests were chosen in order to capture various aspects of reading under different conditions.

To subjectively assess reading and reading effort, we will administer a questionnaire about reading habits that was developed specifically to evaluate the extent to and frequency with which an individual engages in reading activities during activities of daily living, including reading for entertainment or education. Our team has previously employed this measure [50]. It includes questions on language background (eg, first language, language proficiency), assessed self-reported proficiency in reading (1=no ability, 5=fluent ability), reading habits before and after onset of low vision (eg, frequency, enjoyment, type of reading), and enjoyment of reading. In order to evaluate the subjective experience of reading effort, participants will be

asked: “When considering your vision, is reading easy, somewhat difficult, very difficult, or impossible?”

To objectively measure reading performance of short individual sentences, participants will read the English or French version of the Minnesota Low Vision Reading Test chart [91], a clinical assessment chart that allows for the measurement of reading acuity (smallest print read), reading speed (in words per minute), critical print size (smallest print at which reading speed is still optimal), and the Reading Accessibility Index [92], which considers reading ability over a range of print sizes. Its test-retest reliability has been reported at $r=.88$ [92-94].

In order to measure sustained reading of text in paragraph format, participants will be asked to read English or French paragraphs from the International Reading Speed Test [95]. This measure includes reading comprehension questions that have previously been developed and used in our lab in the context of a low vision reading evaluation using the iPad as a magnification device [50]. Its internal reliability has been reported ranging from $a=.77$ to $a=.93$ [95,96].

Finally, we will administer a semantic judgment task using a calibrated computer display, allowing us to capture reaction time and response congruency during a sentence-reading task. Here, participants must first read a sentence (prime) and then see a word (target). Their task is to determine if the target word completes the sentence in a way that makes sense or not. An equal number of congruent and incongruent sentences is included, and dependent variables are accuracy and speed. Sentences chosen for this task all have established completion and Cloze probability norms ([97] for the French and [98] English sentences). During this task, we obtain measures on response speed and accuracy, allowing us to evaluate reading speed, vocabulary comprehension, and ability to judge semantic congruency.

Participant Characteristics

Hearing ability will be assessed as part of the protocol because hearing has been identified as a risk factor for cognitive impairments [4]. We designed the cognitive assessment procedure in such a way that vision is not required for the administration of the auditory testing materials. We will document the ambient sound levels during testing using the Decibel X app by SkyPaw Co Ltd (Hanoi, Vietnam), because testing may be conducted in participants' homes. Ambient noise levels will be used to statistically explore potential noise effects on hearing thresholds. For individuals who experience difficulties hearing the experimental protocol instructions, a Williams Sound Pocketalker (Eden Prairie, MN [99]) will be used to provide amplification.

The integrity of the ear canal will be inspected using the Welch Allyn 22820 PocketScope Otoscope, and the presence of any abnormalities (eg, impacted cerumen, collapsing canals) will be noted.

Participants for whom a recent audiogram is not available in the rehabilitation file will complete a pure-tone audiogram administered using a portable audiometer (Maico MA41, Berlin, Germany, from GénieAudio, Laval, Quebec) with Radioear DD45 earphones. We will use the audiometric results to

calculate the PTA dB HL threshold across 0.5, 1, 2, and 4 kHz in each ear. The PTA will be used to determine which participants become part of the DSI group.

Speech-in-noise thresholds will be measured using the Canadian Digit Triplet Test, validated both in Canadian English and French [100,101]. During this test, participants listen under headphones to triplets of spoken digits (eg, 2, 9, 5) presented in the presence of matched speech-spectrum background noise. The listener can respond nonverbally by entering the digits that have been heard on a numeric keypad or verbally so the tester can enter the responses on the keypad. The Canadian Digit Triplet Test uses an adaptive procedure to compute a speech reception threshold in noise, defined as the signal-to-noise ratio at which the triplets are recognized 50% of the time. There is a high level of consistency across the English and French versions of the test [101]. The more negative the score, the more noise the listener can tolerate.

Participants will complete the Hearing Handicap Inventory for the Elderly questionnaire [102,103] and answer 3 individual questions about hearing ability, which assess their perception of difficulties with activities of daily living that require hearing [102]. These hearing assessments are the same as those that have been used or are planned for the Canadian Longitudinal Study on Aging [104], thereby allowing us to compare our intervention findings to national population data. The Hearing Handicap Inventory for the Elderly explores self-reported situational and emotional hearing abilities and has a reliability coefficient ranging from .88 to .95 and test-retest reliability of $r=.84$ [102,105].

The onset of age-related vision loss due to AMD is often accompanied by a multitude of emotional responses that can potentially interfere with the success of low vision rehabilitation [106,107]. Therefore, the Depression, Anxiety and Stress Scale [108] will be included in the protocol in order to identify individuals whose rehabilitation outcomes might be influenced by their psychological state; however, they are not excluded depending on this measure. This 21-item questionnaire shows excellent psychometric properties, with an internal reliability

ranging from $a=.86$ to $a=.90$ and has been validated in both English and French [109,110].

As part of any low vision exam, the eye care professionals within each rehabilitation center record key variables in the rehabilitation charts. These data will be available for extraction by the research team as described in the study consent and will be extracted at the beginning and end of the study. They include, but are not limited to, diagnoses (ocular and otherwise), monocular and binocular visual acuity (distance vision using ETDRS [111] and contrast sensitivity [Mars chart] [112]), visual field diameter (Octopus perimeter), type and duration of rehabilitation services provided (eg, computer rehabilitation, orientation & mobility services), and type of assistive devices that were prescribed and provided (please note that these devices are provided at no cost to the individual through Quebec Health Insurance/Régie de l'assurance maladie du Québec; therefore, income is not a barrier to device use). The file contains information about the type, frequency, and intensity of vision rehabilitation strategies that were implemented and trained (eg, provision of improved lighting, strategies to read while placing materials on reading stands at the appropriate distance).

In addition, the file contains basic demographic information (eg, presenting gender, age, living situation), as well as a record of all parallel services that were accessed (eg, participation in the day center service, provision of hearing rehabilitation). These clinical variables will be available to the research team for statistical control and analysis.

Participant Timeline

Figure 1 illustrates the structure and timeline of the study. After intake, but before intervention begins, participants will complete the initial administration of all assessment measures. At 6 months and 12 months after the initial rehabilitation appointment, the research assistants will meet with each participant (at home for rehabilitation participants, in the lab with control participants) to repeat the administration of all measures. After the 12-month follow-up, data will be extracted from the rehabilitation charts detailing all rehabilitation interventions. A detailed overview of this process is presented in Figure 2.

Figure 1. Overview of the study structure, timeline, and variables to be measured.

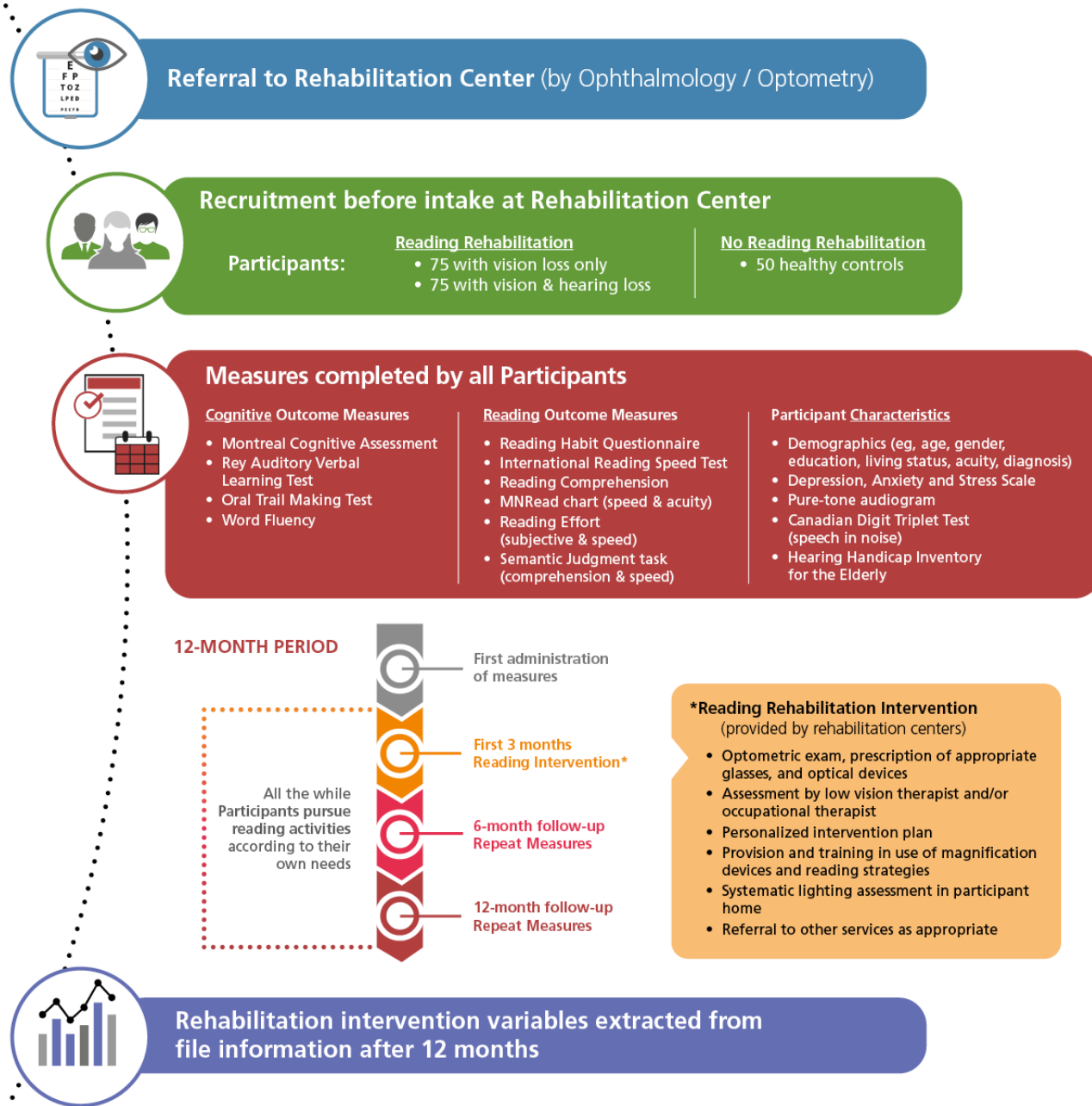


Figure 2. Protocol schedule and procedures. N/A: not applicable.

Activity	Staff	Time to complete (min)	Prestudy screening	Prefest	6-month Follow-up	12-month Follow-up	Chart data extraction
Recruitment	Rehabilitation center staff	5	X				
Consent	Research assistant	5	X				
Montreal Cognitive Assessment	Research assistant	10		X	X	X	
Rey Auditory Verbal Learning Test	Research assistant	10-15		X	X	X	
Oral Trail Making Test	Research assistant	5-10		X	X	X	
Word Fluency	Research assistant	5		X	X	X	
Reading Habits Questionnaire	Research assistant	5		X	X	X	
Minnesota Low Vision Reading Test	Research assistant	5-10		X	X	X	
International Reading Speed Test	Research assistant	2		X	X	X	
Semantic judgment task	Research assistant	5-10		X	X	X	
Otoscopy	Research assistant	3		X	X	X	
Audiogram	Research assistant	5-10		X	X	X	
Canadian Digit Triplet Test	Research assistant	5		X	X	X	
Hearing Questionnaire	Research assistant	10		X	X	X	
Depression, Anxiety and Stress Scale	Research assistant	5-10		X	X	X	
Clinical vision variables	Research assistant	N/A	X				X
Demographic information	Research assistant	N/A	X				X

Sample Size

The power analysis for this study is centered around the MoCA, the primary outcome measure of cognition. We are only aware of 1 study reporting MoCA scores (in its blind version) after a vision rehabilitation intervention, whereby 21 older adults participated in a program evaluation [80]. This study, however, contained reading rehabilitation in addition to various other interventions (eg, orientation and mobility, social engagement in an adapted day center); therefore, the reported effect size of $d=0.794$ (η^2 equivalent=0.136) after 6 months likely overestimates the outcomes we would expect in our study design. To be conservative, we halved this expected effect size for our power estimate. Please note that our control group is primarily used to examine possible practice effects and to observe variability on the measures in a cohort with potentially high age. We based our power analysis on a 3x3 (group x time point) within-between design for analysis of variance. Using gPower [113], a minimum sample size of $n=81$ will allow us to detect small effect sizes of .20 or greater, with an alpha of .05 and a desired power of .95. We also expect an attrition rate of around 10% at each time point based on our previous research with older, visually impaired adults [114,115]. We plan to include covariates in the analyses that will be identified from the analyses linked to the tertiary objective exploring factors that may influence the cognitive benefits of reading rehabilitation. The sample will need to be sufficiently large for these variables to be normally distributed in each group. Therefore, a sample goal of 225 (150 participants with sensory loss, 75 controls) should be sufficient for our protocol. This goal is feasible given an average of 3000 new referrals to rehabilitation in Montreal per year.

Recruitment

Our partner organizations will conduct recruitment for participants in the intervention groups (AMD-only and DSI) as part of their responsibility on the research team. We will recruit control participants through staff of the partner organizations, from family members of participants, as well as through open advertisements in public media and communications to senior groups. In addition, we have access to the Banque des participants of the Centre de recherche institut universitaire de g eriatric de Montreal ($n>1000$). Using this database, we can match our control participants to the intervention participants on variables such as age (by decade), presenting gender, education, and other potential variables of interest, such as MoCA score. Our pilot study [66,67] indicated that we will be able to recruit at least 3 AMD or DSI participants per week, making the recruitment target goal feasible to achieve within 18 months.

Data Collection Methods

Data will be collected by 4 trained research assistants (2 teams of 2 people). The composition of the pairs who work together to collect the data will continuously rotate in order to facilitate harmonization among the teams and ensure consistency and accuracy in the administration of the measures. It will not be possible to conceal group membership from the research assistants because the administration of some of the measures will determine if participants are considered to have a hearing impairment. In addition, control participants will be identifiable because they are not visually impaired. However, the teams will be independent of the administration of the intervention, which will be provided by rehabilitation professionals outside of the research team. Administration of the measures will be

audio-recorded throughout several of the tasks to ensure the highest level of precision and quality control for data entry and to improve testing efficiency and reduce testing time. We offer participants the choice of coming to the lab space at either rehabilitation center or receiving a home visit for data collection. Therefore, we developed our protocol to be easily portable such that the necessary measures and materials can be transported wherever needed by the research team using a wheeled carry-on suitcase.

Data Management

In line with the data management requirements of the Institutional Review Board that approved this protocol and the recommendations by Michener for data management [116], all data will be anonymized and entered in a central password-protected Excel file that will be stored on the encrypted server of the Université de Montréal. Data integrity and quality control will be enforced through random spot-checking by a second member of the team. The data will be accessible for the period of the study approval, plus an additional 5 years thereafter, at which point all electronic and paper files will be destroyed.

Statistical Methods

Planned Analyses

Table 2 provides an overview of the planned analyses. We will examine change in the primary outcome measures (ie, MoCA, reading speed, reading comprehension, subjective report of effort) from baseline over time using generalized linear mixed-effect model analysis employing the *lme4* package [117] and the *bobyqa* optimizer in RStudio [118]. For all primary outcomes, we will assess normality using a visual inspection of the quantile-quantile plot and the Shapiro-Wilk test using the function *shapiro.test*.

In comparison to traditional parametric statistics (ie, analyses of variance), mixed-effect models are relatively robust to violations of normality [117]. Generalized linear mixed-effect model analysis can accommodate nonnormally distributed

responses or dependent variables and categorical data via their variety of family functions. Each measure will be specified as a continuous dependent variable and examined as a *gamma* model (if outcome measure data are skewed) or *gaussian* model (if data are normally distributed) in the family argument of the *glmer* function as a function of the 2 categorical predictors: group (ie, low vision, DSI, control) and time of testing (ie, before, 6 months after, and 12 months after reading rehabilitation), and their interaction. All generalized linear mixed-effect model analyses will include the maximal random effects structure justified by the experimental design [119]. They will include all main effects and interactions of our 2 predictors, group and time of testing, as well as by-subject and by-item random intercepts and random slopes for all relevant main effects. We will exclude random correlations this model. The 95% confidence intervals will be calculated for all estimates (using the *broom* package and *Wald* method in RStudio [118]). In addition, we will account for small imbalances in numbers of the predictors' levels (due to participants not completing all aspects of the test) by entering all predictors in mean-centered form (ie, deviation coding). All entered predictors will be checked for collinearity (using the *cor* function and model output in RStudio). Lastly, we will use post-hoc likelihood-ratio (X^2) model comparisons to quantify the predictive power and exact significance level of all initially significant or trending effects (ie, $P < .1$) revealed by the generalized linear mixed-effect models analyses, as well as the Akaike information criterion. The analyses will include consideration of potential moderators or confounders (ie, presenting gender, age, education). Where significant differences are observed within the primary dependent variables, post-hoc comparisons between groups and level of impairment will calculate unbiased effect sizes, their exact 95% confidence intervals, and Bayes factors [120]. Along with the confidence intervals, a Bayes factor analysis will allow us to quantify the strength of the evidence in support of the null hypothesis if no difference between groups exists. Due to a lack of previous research using Bayes factors in this area, we will use an uninformed prior for the Bayes analysis with a Cauchy width of 0.7.

Table 2. Variables, measures, and methods of analyses.

Variable or outcome	Hypothesis	Outcome measure(s)	Method(s) of analysis
Primary			
Global cognitive function	Improves outcomes at 6 months, maintained at 12 months	Montreal Cognitive Assessment	Mixed effect models, post-hoc analyses, effect sizes, Bayes factors
Reading speed	Improves outcomes at 6 months, maintained at 12 months	Minnesota Low Vision Reading Test, International Reading Speed Test	Mixed effect models, post-hoc analyses, effect sizes, Bayes factors
Reading comprehension	Improves outcomes at 6 months, maintained at 12 months	Comprehension questions of International Reading Speed Test	Mixed effect models, post-hoc analyses, effect sizes, Bayes factors
Perceived effort	Improves outcomes at 6 months, maintained at 12 months	Reading Habit Questionnaire	Mixed effect models, post-hoc analyses, effect sizes, Bayes factors
Secondary			
Reading acuity	Improves outcomes at 6 months, maintained at 12 months	Minnesota Low Vision Reading Test	Mixed effect models, post-hoc analyses, effect sizes, Bayes factors
Critical print size	Improves outcomes at 6 months, maintained at 12 months	Minnesota Low Vision Reading Test	Mixed effect models, post-hoc analyses, effect sizes, Bayes factors
Reading accuracy	Improves outcomes at 6 months, maintained at 12 months	Semantic judgment task	Mixed effect models, post-hoc analyses, effect sizes, Bayes factors
Subjective reports of changes in reading habits	Improves outcomes at 6 months, maintained at 12 months	Reading Habit Questionnaire	Mixed effect models, post-hoc analyses, effect sizes, Bayes factors
Episodic learning	Improves outcomes at 6 months, maintained at 12 months	Rey Auditory Verbal Learning Test	Mixed effect models, post-hoc analyses, effect sizes, Bayes factors
Memory encoding, storage, and retrieval	Improves outcomes at 6 months, maintained at 12 months	Rey Auditory Verbal Learning Test	Mixed effect models, post-hoc analyses, effect sizes, Bayes factors
Attention, speed, and mental flexibility	Improves outcomes at 6 months, maintained at 12 months	Oral Trail Making Test	Mixed effect models, post-hoc analyses, effect sizes, Bayes factors
Semantic fluency	Improves outcomes at 6 months, maintained at 12 months	Word Fluency: FAS & animal naming	Mixed effect models, post-hoc analyses, effect sizes, Bayes factors
Correlations among sensory and cognitive variables	Improved outcomes are positively correlated	All measures	Pearson and Spearman correlation coefficients
Tertiary			
Demographic variables	Influence the cognitive benefits of reading rehabilitation, with varied directionality	Clinical chart review	Covariate in mixed effect models
Hearing impairment severity	Increase in hearing impairment reduces cognitive benefit of reading rehabilitation	Audiogram, Canadian Digit Triplet Test, Hearing Questionnaire	Covariate in mixed effect models
Mental health	Decrease in mental health reduces cognitive benefit of reading rehabilitation	Depression, Anxiety and Stress Scale	Covariate in mixed effect models

Exploratory Analyses

It is likely that some participants will self-select not to complete the follow-up or to abandon parts of the recommended intervention tools and techniques. Therefore, we will examine differences in participant characteristics and consider intent-to-treat within the statistical analyses. These analyses will also explore whether the heterogeneity of the sample has possible effects on the outcomes. We are currently exploring additional funding possibilities in order to extend the study period, should the recruitment of a larger sample be required. This increase in available data would also address possible limitations in statistical power for the large number of potential variables to be included in the analyses.

These data may allow us to follow potential exploratory avenues of analysis. First, if the recruited participants naturally divide into groups with different degrees of change in reading (eg, individuals whose self-reported reading effort was reduced or whose reading activity increased versus those for whom we do not observe a change in reading behavior), we can compare these 2 groups directly, while still considering factors such as hearing status or presenting gender. Second, if no such clear division occurs but participants naturally distribute along a continuum of reading effort and reading behavior variables, we can simply use the secondary reading outcome measure(s) as predictors to test whether any or all of the reading effort measures emerge as significant covariates and examine whether scores on the primary cognitive outcome measures improved over time across our 3 groups, after removing the effect of rehabilitation on reading. Third, if the amount and type of data allow, we will use latent factor analysis to explore whether specific clusters of variables are specifically associated with improvements in reading ability or improved performance on cognitive tests.

In line with the requirements of our funding agencies, both sex and gender were considered during study planning [121]. The present study will not include any biological measures of sex; however, with regards to presenting gender, we will pay specific attention to the binary men:women ratio in the sample as recruitment will likely result in a larger number of women who will participate, given their increased lifespan and larger numbers in vision rehabilitation settings [78]. In addition, gender differences in openness to the acceptance and use of assistive technology have been reported [122-124], which can directly affect the potential benefit of reading rehabilitation approaches that include electronic magnification (eg, the use of an iPad [50,51]). Therefore, presenting gender will feature prominently in our statistical analyses.

Research Ethics Approval

The Comité d'éthique de la recherche of the Centre de recherche interdisciplinaire en readaptation du Montreal metropolitain (CRIR#1284-1217) has provided institutional review board approval. This committee is responsible for research protocols involving recruitment from and testing on the sites of the local clinical partners for this study. The principal investigator will obtain renewal of the ethics approval annually. We submitted all aspects of the study design and data analysis as a stage 1

pre-registered report (ClinicalTrials.gov ID: NCT04276610; February 19, 2020).

Protocol Amendments

Any necessary changes to the protocol (eg, safety and security measures necessary due to COVID-19) are planned in collaboration with the partner sites in order to adhere to the requirements of the Quebec Ministry of Health. These updates and amendments are the submitted for approval to the Comité d'éthique de la recherche of the Centre de recherche interdisciplinaire en readaptation du Montreal metropolitain.

Consent

One of the 4 trained research assistants will obtain written informed consent at the first in-person meeting, either in the home or at the lab in the partner sites. Consent forms are available in large print in both English and French. Participants are free to abandon the study at any time, and this choice will not affect their care at the study partner sites.

Confidentiality

All electronic study data will be stored in a password-protected Excel file on an encrypted server at the Université de Montréal and can only be accessed through a password-protected computer in a locked lab space. All records that contain personal identifiers, such as consent forms and questionnaires, will be stored separately from study records. Each participant file will be identified by code number. Study data will not be released to anyone outside the research team.

Access to Data

Data access is limited to the members of the research team and their trainees. In order to ensure confidentiality, the data that will be available to the research team members will only contain deidentified information.

Ancillary and Posttrial Care

All participants will be rehabilitation clients of 1 of the 2 partner sites. Therefore, they will have access to all available service and referral pathways that are part of the care offer. Should the research team suspect or a participant express a potential need for services or referral (eg, counseling), the research team will connect the participant with their respective rehabilitation file manager at the partner site for follow-up.

Dissemination Policy

All members of the research team have the right to access and analyze all data, for the purpose of dissemination. The principal investigator will oversee dissemination activities in order to ensure that team members with the necessary topic expertise are involved in each aspect of dissemination. Study results will be made available in open-access format whenever possible and will be presented in formats that are accessible to researchers, clinicians, policy makers, members of the public, participants, and all other stakeholders. The study also distinguishes itself with its multifaceted approach to integrated knowledge translation and dissemination. The clinical partners are represented on the research team, directly influencing the study and maintaining the clinical relevance of the study goals. They are part of a local network of rehabilitation research sites, the

Center for Interdisciplinary Rehabilitation Research of Greater Montreal [125], providing the research team a unique opportunity to disseminate their knowledge translation activities that are planned to occur after the study is completed. As an extension of this network, established collaborations with the Sense-Cog group in Europe [126], Envision University in the United States [127], and Canadian Consortium on Neurodegeneration in Aging knowledge translation team [128] provide access to sensory-cognitive-specific knowledge translation opportunities that will facilitate the distribution and implementation of our findings. Furthermore, Dr. Swenor, as a visually impaired scientist [129] and team member, brings a unique and important knowledge translation, equity, and inclusion perspective to the study. Finally, all collaborators and partners will participate in the development of a Canadian Institutes of Health Research Café scientifique [130] at study completion. This type of public, open science dissemination event is designed to disseminate the results at a clinical level and inform stakeholders as well as participants and their friends and family of the study outcomes

Results

The Fonds de recherche Quebec - Santé & Fondation Turmel funded the first 2 years of this peer-reviewed protocol (see [Multimedia Appendix 1](#)). The Canadian Institutes of Health Research provided a Project Grant within a Patient-Oriented Research Priority Announcement for a third year. We submitted all aspects of the study design and data analysis as a stage 1 pre-registered report (ClinicalTrials.gov ID: NCT04276610; February 19, 2020). The Comité d'éthique de la recherche of

the Centre de recherche interdisciplinaire en readaptation du Montreal metropolitain (CRIR#1284-1217) has provided institutional review board approval. This committee is responsible for research protocols involving recruitment from the clinical partners (local sensory rehabilitation centers) within this study: the Centre de réadaptation Lethbridge-Layton-Mackay du Centre intégré universitaire de santé et de services sociaux du Centre-Ouest-de-l'Île-de-Montréal and the Institut Nazareth et Louis-Braille du Centre intégré de santé et de services sociaux de la Montérégie-Centre. Recruitment began on April 24, 2019. As of March 13, 2020, 38 low vision participants and 7 control participants had been enrolled. Recruitment was paused due to lock-down on March 13, 2020 and will recommence once the COVID-19 crisis has passed to a point where face-to-face data collection with older adults becomes feasible again.

Discussion

To our knowledge, this study protocol is the first to propose the exploration of the potentially beneficial effect of reading rehabilitation on cognitive functioning in older adults with AMD. Both vision and hearing impairments were recently specifically mentioned as variables that should be considered in the assessment of cognitive functioning [5]. Therefore, given the current trends in the global aging of the population and the emerging importance of sensory health for cognitive health [3], the timing of this study is optimal in order to elucidate whether reading rehabilitation may be able to reduce the potential risks that vision impairment poses for declines in cognitive functioning.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer Review Comments by the Fonds de recherche Quebec - Santé (funding for Year 1 and 2) and Canadian Institutes of Health Research (year 3) committees.

[\[PDF File \(Adobe PDF File\), 194 KB - resprot_v10i3e19931_app1.pdf\]](#)

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Abbreviations

AD: Alzheimer's disease
AMD: age-related macular degeneration
dB HL: decibel hearing level
DSI: dual sensory impairment
MMSE: Mini-Mental State Examination
MoCA: Montreal Cognitive Assessment
PTA: pure-tone average
RAVLT: Rey Auditory Verbal Learning Test

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Protocol

Intermittent Versus Continuous Low-Energy Diet in Patients With Type 2 Diabetes: Protocol for a Pilot Randomized Controlled Trial

Sarah McDiarmid^{1*}, RD, MMath; Michelle Harvie^{1*}, RD, PhD; Rhona Johnson², RGN, RSCN; Avni Vyas¹, RD, MPhil; Aza Aglan³, PhD, ClinPsyD; Jacqui Moran², RD; Helen Ruane¹, BSc; Amanda Hulme², RGN, BSc; Katharine Sellers¹, BSc; Basil Issa^{2*}, MD, FRCP

¹The Prevent Breast Cancer Research Unit, Manchester University NHS Foundation Trust, Manchester, United Kingdom

²Department of Endocrinology and Diabetes, Manchester University NHS Foundation Trust, Manchester, United Kingdom

³Greater Manchester Mental Health Foundation Trust, Manchester, United Kingdom

*these authors contributed equally

Corresponding Author:

Sarah McDiarmid, RD, MMath

The Prevent Breast Cancer Research Unit

Manchester University NHS Foundation Trust

Southmoor Road

Wythenshawe Hospital

Manchester, M23 9LT

United Kingdom

Phone: 44 1612914412

Fax: 44 1612914421

Email: sarah.mcdiarmid@mft.nhs.uk

Abstract

Background: Intensive face-to-face weight loss programs using continuous low-energy diets (CLEDs) providing approximately 800 kcal per day (3347 kJ per day) can produce significant weight loss and remission from type 2 diabetes (T2D). Intermittent low-energy diets (ILEDs) and remotely delivered programs could be viable alternatives that may support patient choice and adherence.

Objective: This paper describes the protocol of a pilot randomized controlled trial to test the feasibility and potential efficacy of remotely supported isocaloric ILED and CLED programs among patients with overweight and obesity and T2D.

Methods: A total of 79 participants were recruited from primary care, two National Health Service hospital trusts, and a voluntary T2D research register in the United Kingdom. The participants were randomized to a remotely delivered ILED (n=39) or CLED (n=40). The active weight loss phase of CLED involved 8 weeks of Optifast 820 kcal/3430 kJ formula diet, followed by 4 weeks of food reintroduction. The active weight loss phase of ILED (n=39) comprised 2 days of Optifast 820 kcal/3430 kJ diet and 5 days of a portion-controlled Mediterranean diet for 28 weeks. Both groups were asked to complete 56 Optifast 820 kcal/3430 kJ days during their active weight loss phase with an equivalent energy deficit. The diets were isocaloric for the remainder of the 12 months. CLED participants were asked to follow a portion-controlled Mediterranean diet 7 days per week. ILED followed 1-2 days per week of a food-based 820 kcal/3430 kJ diet and a portion-controlled Mediterranean diet for 5-6 days per week. Participants received high-frequency (weekly, fortnightly, or monthly depending on the stage of the trial) multidisciplinary remote support from a dietitian, nurse, exercise specialist, and psychologist via telephone or the Oviva smartphone app. The primary outcomes of the study were uptake, weight loss, and changes in glycated hemoglobin at 12 months. An outcome assessment of trial retention was retrospectively added. Secondary outcomes included an assessment of adherence and adverse events. A qualitative evaluation was undertaken via interviews with participants and health care professionals who delivered the intervention.

Results: A total of 79 overweight or obese participants aged 18-75 years and diagnosed with T2D in the last 8 years were recruited to the Manchester Intermittent and Daily Diet Diabetes App Study (MIDDAS). Recruitment began in February 2018, and data collection was completed in February 2020. Data analysis began in June 2020, and the first results are expected to be submitted for publication in 2021.

Conclusions: The outcomes of the MIDDAS study will inform the feasibility of remotely delivered ILED and CLED programs in clinical practice and the requirement for a larger-scale randomized controlled trial.

Trial Registration: International Standard Randomized Controlled Trial Number (ISRCTN) 15394285; <http://www.isrctn.com/ISRCTN15394285>

International Registered Report Identifier (IRRID): DERR1-10.2196/21116

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KEYWORDS

type 2 diabetes; diabetes; diabetic diet; low-energy diet; low calorie diet; intermittent energy restriction; intermittent fasting; diabetes remission; smartphone; mobile phone; mHealth; mobile health

Introduction

Background

An estimated 4.7 million people have type 2 diabetes (T2D) in the United Kingdom, with the number expected to rise to over 5.5 million by 2030 [1]. Diabetes related complications are common, and people with T2D die up to 10 years earlier than those without the disease [2]. Currently, 10% of the National Health Service (NHS) budget in the United Kingdom is spent on diabetes (approximately £10 billion (US \$13.8 billion) per year) [1].

Approximately 80% to 90% of people with T2D have overweight or obesity [3-6]. Clinical guidelines for the management of T2D focus largely on multiple drug treatments to reduce blood glucose. They also recommend at least 5% to 10% weight loss [7,8] as this leads to improvements in glycemic control, insulin sensitivity, blood lipids, and blood pressure (BP) [9,10].

Continuous and Intermittent Low-Energy Diets

Intensive face-to-face weight loss programs using continuous low-energy diets (CLEDs) that provide approximately 800 kcal (3347 kJ) per day of formula-based total diet replacement for 8 to 20 weeks or longer are highly effective for large weight loss and remission from T2D [11-14]. The recently published Diabetes Remission Clinical Trial (DiRECT) tested an intensive CLED program in primary care and found that it was superior to standard best practice care (standard daily moderate energy restriction advice with minimal support). At 12 months, 45.6% (68/149) participants of the intervention group achieved remission with an average weight loss of 10 kg compared with 4.0% (6/149) and 1 kg loss in the control group ($P < .001$). Remission was highest (31/36, 86%) in those who achieved 15% weight loss [13] and is more likely in those diagnosed with T2D in more recent years [15].

The CLED approach using total diet replacement is thought to be effective because the initial rapid weight loss can be highly motivating [16], and formula diets remove decision making around food choices. In addition, subjective hunger may be reduced by the associated ketosis [17]. CLEDs have been shown to reduce excess fat in the liver and pancreas in patients with T2D, which is part of the proposed mechanism for T2D remission [11,18].

Possible drawbacks of the CLED approach are that it is not appealing to or achievable for everyone. Participants following CLED programs report shame and awkwardness in social situations centered around food [19]. Attrition in intensive

CLED studies on people with overweight or obesity (+/-T2D) is approximately 25% [13,20], although higher rates have been reported in studies with less frequent health care professional (HCP) contact [14]. The prevention of weight gain following a CLED program remains a key challenge. In 2 years, participants in the CLED group in the DiRECT trial appeared to have regained approximately 40% of the weight they had lost after the initial total diet replacement phase despite regular face-to-face support and an intensive 2-year relapse program involving repeated spells of a CLED, partial meal replacements, and antiobesity medications [13,21].

An intermittent low-energy diet (ILED) is a potential alternative to CLED. This includes the same number of low-energy formula diet days as CLED, but these days are undertaken for 2 days per week over a longer period. ILED may provide an alternative approach for people who find CLEDs unappealing or difficult to maintain. Qualitative reports on people following CLEDs suggest that they would prefer an intermittent approach that may be easier to fit into life without the need for weeks away from normal food [22].

A recent randomized controlled trial (RCT) in people with T2D compared an ILED with regular, daily, modest energy restriction (1200-1500 kcal/5020-6276 kJ per day) for 12 months and showed similar improvements to glycemic control in both groups [23]. Early studies of CLEDs show that some of the improvements in insulin sensitivity and beta cell function are associated with acute energy restriction rather than weight loss [24]. As these benefits subsequently attenuate when subjects enter weight maintenance with euenergetic feeding [25], ongoing spells of intermittent energy restriction each week may be a way to maintain beneficial glycemic control. A recent RCT ($n=46$) of participants with prediabetes and overweight or obesity showed that an ILED every other day for 12 months produced greater reductions ($P < .05$) in fasting insulin -52% (SE 9%) and insulin resistance -53% (SE 9%) compared with isocaloric daily moderate calorie restriction (-14%, SE 9%; -17%, SE 11%) despite similar decreases in body weight [26].

An ILED with 2 low-energy days per week will lead to a slower initial weight loss compared with a CLED. An unanswered research question is whether an ILED may lead to improved weight loss maintenance compared with daily dietary approaches in patients with T2D.

The relative benefits of ILED versus isocaloric CLED regarding glycemic control, diabetes remission, and weight loss maintenance in people with T2D are unknown.

Remote Follow-up

A potential strategy for increasing adherence efficacy and reach of low-energy diet (LED) programs may be to include high-frequency remote follow-up, which has been shown to be superior to low frequency face-to-face care in weight management interventions [27]. Remote care reduces participants' burden of attending face-to-face appointments and may be cost-effective compared with face-to-face care [28] while improving access to care. There is growing evidence to support the use of telehealth (including telephone and mobile phone-based apps) to monitor and provide feedback to patients with T2D and promote self-management of their condition [29-31].

The Manchester Intermittent versus Daily Diet Diabetes App Study (MIDDAS) incorporated high-frequency remote follow-up via the Oviva smartphone app and by telephone [32]. The app was used to facilitate self-monitoring of diet, weight, and blood glucose, and communication with HCPs, with the option of remote peer group support. Group participation in mobile apps has been shown to predict weight loss success [33]. Remote communities can be encouraging, motivating, and informative while remaining convenient and anonymous [34].

Goals of This Study

The primary aim of MIDDAS is to assess the feasibility and potential efficacy of remotely supported ILED and isocaloric CLED programs in patients with overweight or obesity and T2D. The feasibility of an RCT comparing the 2 approaches was also assessed. MIDDAS did not have a control group for comparison because CLED programs have already been shown to be superior to standard or best practice.[13] The initial estimates of acceptability (uptake and retention) and potential efficacy (change in weight and glycated hemoglobin [HbA_{1c}]) of the programs will determine whether progression to a full RCT is indicated and will inform the feasibility of delivering ILED and CLED programs that incorporate remote follow-up.

Methods

The trial protocol (V5.0/08.04.19) was granted ethical approval by the North West Greater Manchester South Research Ethics

Committee (ref:17/NW/0389). SPIRIT reporting guidelines were used [35].

Design and Setting

The study was a 12-month pilot 2-arm RCT, performed in patients with T2D and overweight or obesity, recruited from general practices, NHS hospital trusts and an NHS-supported voluntary research register in England. Participants attended trial assessments at Manchester University NHS Foundation Trust (MFT), Manchester, United Kingdom. Participants received dietary support remotely via the Oviva app and/or by telephone.

Recruitment

Potential eligible participants were recruited from 3 settings using the following methods:

1. Patients in three general practices in Manchester were sent targeted invite letters and a text message reminder 8 weeks later if there was no response. These practices included a population of patients with T2D ranging from 400 to 700 and reflected different levels of deprivation in England. The England Index of Multiple Deprivation (IMD) score for each practice was 10.9 (least deprived 25% in England) and 29.8 and 44.1 (top 25% deprived in England) [36].
2. Patients at MFT and Stockport NHS Foundation Trust were invited to the study via patient record search and invitation letter, using poster displays, or during face-to-face routine clinical contacts.
3. Patients with T2D (n=2500) on the Help BEAT Diabetes volunteer database (hosted by the National Institute of Health Research Clinical Research Network for Greater Manchester) were contacted via mail or email and asked to check if they met the eligibility criteria for the trial and to contact the MIDDAS trial team if they were interested in taking part.

Those invited by letter had the opportunity to tell the trial team why they did not wish to take part via an anonymous reply slip. Interested patients were invited to an optional group session at MFT to receive more information on the diets and try the Optifast meal replacements before deciding to participate.

The inclusion and exclusion criteria for the trial is detailed in [Textbox 1](#).

Textbox 1. Inclusion and exclusion criteria.

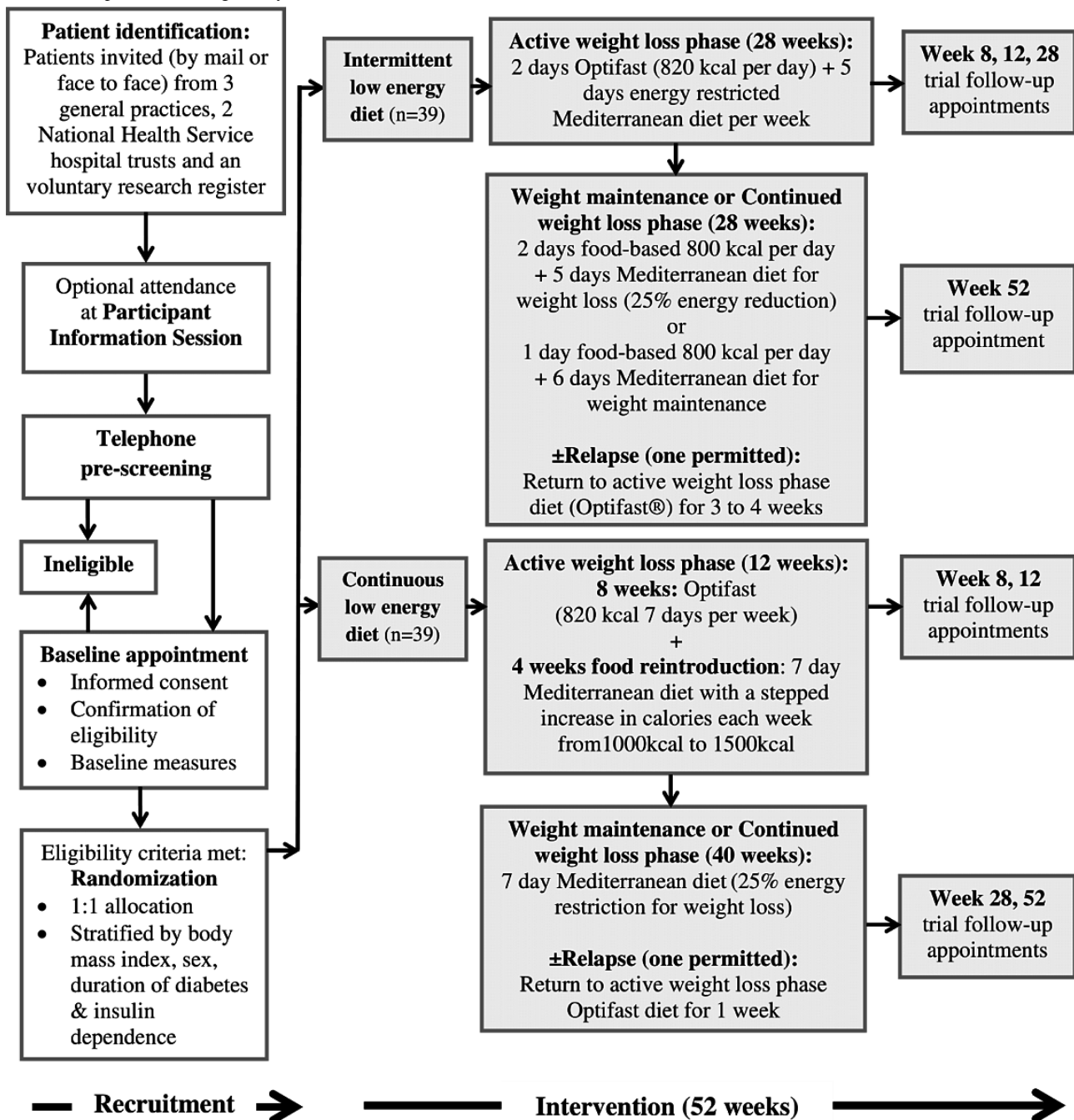
<p>Inclusion criteria</p> <ul style="list-style-type: none">• Willing and able to provide written informed consent• Male or female aged between 18 and 75 years• Diagnosed with type 2 diabetes <8 years• Diet controlled only or receiving any type of diabetes medications including insulin• Glycated hemoglobin (HbA_{1c}) ≥48 mmol per mol (6.5%) at baseline (venous blood sample)• BMI >27 kg per m² and <50 kg per m² or >25 kg per m² and <50 kg per m² in high-risk ethnic minority groups (ie, South Asian, Black African, and African Caribbean)• Access to and ability to use the telephone• Willing to be randomized to an intermittent low-energy diet or continuous low-energy diet using total diet replacement drinks <p>Exclusion criteria</p> <ul style="list-style-type: none">• Routine HbA_{1c} ≥108 mmol per mol (12.0%) during the last 3 months• Unstable retinopathy, grade R2 or higher, or no retinopathy screen within the last 12 months• Pregnant or considering pregnancy• Previous bariatric surgery• Current treatment with Orlistat• Unintentional weight loss ≥5 kg within last 6 months• Learning difficulties, lacking capacity or unable to understand English• Known sensitivity to ingredients in the total diet replacement• Diagnosed eating disorder. Severe binge eating or very low eating self-efficacy were assessed using the following questionnaires: Binge Eating Scale (BES [37], score ≥27) and Weight Efficacy Lifestyle Questionnaire Short Form (WEL-SF [38], score ≤35)• Severe anxiety or depression was assessed using the Generalized Anxiety Disorder Scale (GAD-7 [39], score ≥15) and Patient Health Questionnaire-9 (PHQ-9[40], score ≥15). Hazardous or harmful drinking was indicated by the Alcohol Use Disorders Identification Test (AUDIT [41], score ≥16)• Active symptoms associated with emotionally unstable personality disorder, bipolar disorders, psychotic disorders, post-traumatic stress disorder, and current self-harm or suicidal behavior. Participants with these issues were potentially eligible, dependent on further information from their general practitioners and responses to the baseline study questionnaires• Current treatment with lithium, antipsychotics, or other psychotropic medications that may cause excessive weight gain• Chronic use of steroids• Medical conditions that in the opinion of the treating physician were at risk of deterioration (eg, severe systemic or organ disease, active cancer, liver, gall bladder disease, and pancreatitis)• Current participation in a diabetes drug trial

Participant Flow and Medication Management

The participant flow through the study is outlined in [Figure 1](#). Informed consent was obtained by the trial research nurse at

the baseline appointment. Eligible participants were randomized to ILED or CLED. All participants were invited to attend follow-up appointments at MFT for a repeat of clinical measurements at weeks 8, 12, 28, and 52.

Figure 1. Participant flow through study.



Changes to diabetes and antihypertensive medications specific to each treatment arm are detailed in the trial medication management plan in Table S2 of [Multimedia Appendix 1](#). The CLED medication management protocol was devised by the research team and instructed participants to stop all diabetes medications, with the exception of metformin. Insulin was stopped or reduced, depending on the baseline HbA_{1c} level. Medication management of the ILED arm was adapted from a protocol tested in a recent ILED trial [42]. Medications in both arms were reintroduced or titrated during the trial according to clinical needs. General practitioners (GPs) were notified of the enrollment of patients and changes to their medications by letter.

Randomization and Blinding

Eligible participants were randomized 1:1 to ILED or CLED by a researcher independent of the intervention using a minimization program stratified by BMI ≥ 34 or < 34 kg per m² (projected mean value from the counterpoint and counterbalance studies [11,12,15]), sex, duration of diabetes < 4 years or ≥ 4 years, and whether participants were prescribed insulin. Due to the nature of the intervention, it was not possible to blind participants and clinicians to the treatment allocation. Clinical assessments were performed by an independent research assistant. Laboratory results were assessed by independent laboratory staff.

Interventions

Figure 1 shows a summary of the 2 dietary programs. Both included a combination of the Optifast LED and the Mediterranean diet over a period of 12 months. Both programs were designed to have exactly 56 Optifast LED days and an equivalent level of energy restriction during their active weight loss phase and weight maintenance or continued weight loss phase.

CLED

Active Weight Loss Phase (12 weeks)

Weeks 1 to 8 involved the Optifast LED (Nestlé Health Science, United Kingdom). This provided approximately 820 kcal (3430 kJ) per day and consisted of 3 sachets per day of Optifast (200 kcal/837 kJ per sachet of shake or soup made with water) in addition to 8×80 g portions of nonstarchy vegetables (approximately 140 kcal/586 kJ), one dessertspoon of oil per day (80 kcal per 335 kJ), and 2-2.5 liters of calorie-free fluids. The participants were asked to avoid alcohol and excessive caffeine to minimize the risk of dehydration. Participants who were unable to tolerate Optifast were offered a food-based LED with a similar macronutrient profile. This comprised 250 g of lean protein foods (eg, lean meat, fish, eggs, and vegetarian proteins), 5 portions of nonstarchy vegetables, 3 portions of low-fat dairy (eg, 200 ml milk), one portion of unsaturated fat (eg, small handful nuts), one portion of fruit, and one carbohydrate portion (eg, slice of bread). Participants reported their adherence to the LED days throughout the trial during their regular contact with the dietitian.

Diet reintroduction in weeks 9-12 allowed a food-based, energy-restricted Mediterranean diet providing 1000 kcal (4184 kJ) daily in week 1, 1200 kcal (5021 kJ) daily in week 2, 1400 kcal (5858 kJ) daily in week 3, and 1500 kcal (6276 kJ) daily in week 4.

The Mediterranean diet, as described previously by Harvie et al [43], was relatively high in protein (25% energy) with moderate carbohydrate (45% energy from low glycemic load carbohydrates), moderate fat (30% energy from fat: 15% monounsaturated, 8% polyunsaturated, and 7% saturated fatty acids), and limited alcohol to <10 units per week.

Weight Maintenance or Continued Weight Loss Phase (40 Weeks)

Participants who achieved a trial weight loss goal of 15%, and/or their target weight if greater, were advised to follow a euenergetic Mediterranean diet for weight maintenance. Those who had not achieved 15% weight loss or wished to lose more weight were asked to follow a 25% energy-restricted Mediterranean diet. Individuals' estimated energy requirements were calculated using the Mifflin equations [44] to estimate the basal metabolic rate×reported metabolic equivalent of the task. These calculations were based on the revised weight and activity levels after the completion of the active weight loss phase.

ILED

Active Weight Loss Phase (28 weeks)

The ILED group was asked to include 2 consecutive days per week of the Optifast LED plus 5 days of a Mediterranean diet for 28 weeks. An energy deficit was applied to the Mediterranean diet (up to a value of 265 kcal [1109 kJ] per day) to ensure that the ILED and CLED diets were isocaloric during the active weight loss phase.

Weight Maintenance or Continued Weight Loss Phase (24 weeks)

Participants were asked to follow a food-based ILED. Participants who had achieved 15% weight loss, and/or their target weight if greater, were asked to follow the food-based LED described above for one day per week and a euenergetic Mediterranean diet aimed at weight maintenance (eg, 2550 kcal [10,669 kJ] per day for a 50-year-old man, BMI 34) for 6 days. Participants who had not achieved 15% weight loss or wished to lose more weight were asked to follow the food-based LED for 2 consecutive days per week and an energy-restricted Mediterranean diet (eg, 2100 kcal [8786 kJ] per day for a 50-year-old man, BMI 34) for 5 days. This provided an overall daily 25% energy restriction through the week.

Relapse

Trial participants who regained 2 kg or more during their weight maintenance or continued weight loss phase were offered one opportunity to resume their initial active weight loss diet to help reverse the weight gain. The CLED group was offered the 820 kcal (3430 kJ) formula Optifast LED for one week, and the ILED group was offered the Optifast LED 2 days per week for 3 to 4 weeks. The relapse program included increased support and monitoring by the trial dietitian and support from the trial psychologist to explore reasons for weight regain and to prevent further relapse.

Dietitian and Nurse

The diabetes specialist dietitian provided education on the diets and how to use the Oviva app, either by telephone or face-to-face. All participants were provided with written support materials, including recipes and meal plans. The diabetes specialist nurse provided support for patients who were on diabetes medications other than metformin, on antihypertensives, or who were hypertensive at baseline. All changes to diabetes and antihypertensive medications were agreed upon by the trial doctor and communicated to participants and their GP by a diabetes specialist nurse.

Physical Activity

Participants were encouraged to undertake physical activity (PA) throughout the trial to limit the loss of fat-free mass and promote weight loss maintenance. PA was supported by an exercise specialist, and suitability for PA was assessed at baseline using the Physical Activity Readiness Questionnaire (PAR-Q) [45] and signed off by the trial consultant endocrinologist. Participants were encouraged to aim for 5×30 minutes of moderate-intensity cardiovascular PA per week and resistance exercises for the legs, arms, and trunk 3 times per week. They were signposted to local PA services as appropriate.

and were educated on minimizing the risk of hypoglycemia. Diabetes medications were managed alongside exercise in response to the reported blood glucose readings.

Psychological Support

Enhanced psychological support from the trial psychologist was available for participants whose baseline scores indicated moderate scores for binge eating (score 18-26 on BES [37]), self-efficacy (score 36-45 on the Weight Efficacy Lifestyle Questionnaire Short Form (WEL-SF) [38]), anxiety (score 10-14 on the generalized anxiety disorder scale (GAD-7, [39]), depression (score 10-14 on the Patient Health Questionnaire-9 [PHQ-9]; [40]), or risk of alcohol-related problems (score 8-15 on the Alcohol Use Disorders Identification Test [AUDIT]; [41]). Psychological support was also available to participants who relapsed or had been identified by the team as experiencing difficulties impairing their ability to adhere to the programs. Psychological intervention was informed by motivational interviews, cognitive behavioral therapy, behavioral activation, mindfulness, emotional regulation, and distress tolerance skills.

Remote Behavioral Support

All participants received regular remote support from a multidisciplinary team including a diabetes specialist dietitian, nurse, and exercise specialist. The frequency and mode of behavioral support are detailed in Tables S1 and S2 in [Multimedia Appendix 2](#). For example, the dietitian contacted the participants weekly via Oviva app messaging in weeks 1 to 12, fortnightly in weeks 13 to 28, and monthly in weeks 29 to 52. Follow-up telephone calls with the dietitian were performed at weeks 8, 12, 28, and 52.

Participants were invited to communicate with the multidisciplinary team via the Oviva app functional on iOS and Android smartphones and tablets. The app facilitates written messages and self-monitoring of diet, weight, blood glucose, weight, and activity levels. Participants were also invited to take part in group messaging on the app with other participants from their allocated diet group. Use of the app was optional, so if participants chose not to use it, then their scheduled contacts were done by telephone.

Participants signed a treatment contract to monitor their blood glucose and BP according to the protocol (Table S1 in [Multimedia Appendix 1](#)) and reported these values by telephone or via the Oviva app to the multidisciplinary team. The number of participants in both arms who requested face-to-face dietary consultations during the trial was recorded.

The multidisciplinary team was trained in motivational interview techniques (a well-established model of supporting behavioral change with proven efficacy in facilitating weight loss) to support dietary behavioral changes during both LED programs and in the longer term. Both programs used behavior change techniques such as *problem solving* and *feedback on behavior*, identified in a recent systematic review as being effective in reducing HbA_{1c} [46]. The programs also used established

behavior change techniques, such as goal setting and self-monitoring [47].

Outcomes

Primary

1. Uptake: To achieve an uptake of at least 10% from a primary care mail out.
2. The proportion of subjects in the ILED and CLED groups who successfully lost and maintained >15% weight loss at 12 months, as determined by intention-to-treat (ITT) analysis.
3. The proportion of subjects in both groups who achieved HbA_{1c} <48 mmol per mol (6.5%) at 12 months using ITT analysis.
4. Retention: Aiming for a retention of 60% (48/79) completion as measured by attendance at the 12-month appointment. This is the acceptable completion rate in NICE guidance for commissioning weight management services in England [48].

Secondary

Process Measures

1. Participant adherence to the protocol including self-reported adherence to LED days, preference for face-to-face contact with the dietitian, preference for food-based LED days over Optifast, and attendance at follow-up appointments.
2. Download and usage of the Oviva app for self-monitoring.

Exploratory Measures

Change in the following measures across the 12-month study period:

1. Body fat and fat-free mass (bioelectrical impedance)
2. Waist and hip circumference
3. BP, lipid profile, and fasting blood glucose levels
4. Number and dosage of diabetes and BP medications
5. Self-efficacy for eating, anxiety, depression, and quality of life (as measured by WEL-SF [38], GAD-7 [39], PHQ-9 [40] and Audit of Diabetes-Dependent Quality of Life (ADDQoL) [49] questionnaires, respectively)
6. Quality of diet on non-LED days (as measured by the Mediterranean diet score questionnaire [50])
7. PA (as measured by the Scottish Physical Activity Questionnaire [51])
8. Self-reported satisfaction with weight loss was measured using a 7-point Likert scale. This is highly relevant for the comparison of ILED and CLED, where the CLED will experience faster initial weight loss and achievement of their weight loss goal than the ILED arm [52]
9. Serious adverse events reported up to the end of the 12-month trial

Measurements

[Table 1](#) provides a summary of the measurements collected at baseline and weeks 8, 12, 28, and 52 by a research nurse.

Table 1. Schedule of enrollment and assessments.

Schedule	Enrollment	Follow-up visits			
	Baseline	8 weeks	12 weeks	28 weeks	52 weeks
Enrollment					
Informed consent	✓ ^a	— ^b	—	—	—
Eligibility screen	✓	—	—	—	—
Randomization	✓	—	—	—	—
Assessments					
Height	✓	—	—	—	—
Weight	✓	✓	✓	✓	✓
Waist circumference	✓	✓	✓	✓	✓
Hip circumference	✓	✓	✓	✓	✓
Body fat or fat-free mass (impedance)	✓	✓	✓	✓	✓
Blood Pressure, heart rate ^c	✓	✓	✓	✓	✓
Blood lipids, liver function, renal profile	✓	—	—	✓	✓
Fasting plasma glucose	✓	✓	✓	✓	✓
Laboratory HbA _{1c} ^d	✓	—	✓	✓	✓
Pregnancy urine test	✓	✓	✓	✓	✓
BES ^e questionnaire	✓	—	—	✓	✓
AUDIT ^f questionnaire	✓	—	—	✓	✓
WEL-SF ^g questionnaire	✓	—	—	✓	✓
PHQ-9 ^h questionnaire	✓	✓	✓	✓	✓
GAD-7 ⁱ questionnaire	✓	✓	✓	✓	✓
EQ-5D-3L ^j questionnaire	✓	—	—	✓	✓
ADDQoL ^k questionnaire	✓	—	—	✓	✓
Mediterranean diet score	✓	—	✓	✓	✓
S-PAQ ^l , PAR-Q ^m	✓	—	✓	✓	✓
Self-satisfaction with the weight loss question ⁿ	—	✓	✓	✓	✓
Participant qualitative interviews	—	—	✓ (CLED ^o)	✓ (ILED ^p)	—
Health care professional qualitative interviews	—	—	—	—	✓

^aEvent or assessment occurred at this time point.

^bEvent or assessment did not occur at this time point.

^cFurther investigation with an ECG if heart rate <50 beats per minute and not on beta-blockers.

^dHbA_{1c}: glycated hemoglobin.

^eBES: Binge Eating Scale.

^fAUDIT: Alcohol Use Disorders Identification Test.

^gWEL-SF: Weight Efficacy Lifestyle Questionnaire Short Form.

^hPHQ-9: Patient Health Questionnaire scale-9.

ⁱGAD-7: Generalized Anxiety Disorder scale-7.

^jEQ-5D-3L: Measure of health-related quality of life.

^kADDQoL: Audit of Diabetes-Dependent Quality of Life.

^lS-PAQ: Scottish Physical Activity Questionnaire.

^mPAR-Q: Physical Activity Readiness Questionnaire.

ⁿGiven the effort you put into following the diet and exercise plan, how satisfied are you with the amount of weight you have lost or gained during the

past month? 1=very dissatisfied to 7=very satisfied.

^oCLED: continuous low-energy diet.

^pILED: intermittent low-energy diet.

Participant Characteristics

At baseline, we collected information on participants' age, sex, marital status, number of dependents living at home, ethnicity, education history and employment status, IMD score based on their postal code, relevant medical history, and current medications.

Physical Measurements

Weight and body composition were measured using Tanita BC-300MA calibrated scales to the nearest 0.1 kg. Height was measured using a portable stadiometer. Waist circumference was measured halfway between the point of the lowest rib and the iliac crest, and hip circumference was measured at the maximum circumference of the buttocks [53]. All measurements were taken to the nearest 1 mm. BP was measured with patients seated at rest for at least 10 minutes. All assessors were trained in accordance with the departmental protocols.

Fasting Blood Sample

A fasting venous blood sample was collected for HbA_{1c}, plasma glucose, lipid profile, serum urea and electrolytes, eGFR, creatinine, and liver function tests. A urine pregnancy test was performed in women of childbearing age to exclude pregnancy. Pregnant women were excluded from the trial. Laboratory results were assessed by independent laboratory staff.

Questionnaires

The full list of questionnaires referenced in Table 1 is BES [37], WEL-SF [38], GAD-7 [39], PHQ-9 [40], AUDIT [41], PAR-Q [45], ADDQoL [49], Mediterranean diet score [50], Scottish Physical Activity Questionnaire [51], and EQ-5D-3L [54] (standardized validated instrument used to measure general health status). All questionnaires for which a third party does not own the copyright can be found in Multimedia Appendices 3 [37], 4 [38], 5 [39], 6 [40], 7 [41], 8 [45], 9 [50], 10 [51], and 11 [54].

Retention and Withdrawal

Participants had the right to withdraw from the trial at any time. Participants were considered as withdrawn from the trial if they withdrew from the study intervention voluntarily or if they failed to return for follow-up assessments. Participants could also be removed by the principal investigator if this was considered necessary for medical reasons or due to ineligibility arising during the study (eg, pregnancy). Reasons for withdrawal were recorded, and their GP was notified with recommendations for follow-up care where appropriate. Participants who withdrew continued to have weight and HbA_{1c} collected from their routine diabetes clinic or GP visits for the duration of the 12-month trial unless they did not consent to this at baseline. No incentives were provided to the participants to promote retention and follow-up.

Adverse Events

All adverse events in the 12-month study period were recorded by following the Good Clinical Practice and Health Research Authority processes. Nonserious adverse events such as constipation, fatigue, or hair loss were recorded when participants informed the trial team.

Qualitative Evaluation

In-depth semistructured interviews were conducted with a subset of 10 ILED and 10 CLED participants at the end of the active weight loss phase (ILED week 28, CLED week 12). HCPs (n=6) delivering the programs were also interviewed near study completion. All interviews were conducted by an independent research assistant trained in qualitative interview techniques. Interviews explored the participant and HCP experiences of the ILED and CLED programs and the use of the Oviva app. Purposive sampling was used to select trial participants with a range of success in terms of actual weight loss and HbA_{1c} reduction, as well as participants' perceived success. Participants with ethnicities other than White-British were included where possible, with a fairly even split between men and women. All participants gave written informed consent to be interviewed and were assured that their data would be anonymized. The interviews were audiorecorded and transcribed verbatim for thematic analysis.

Sample Size and Statistical Analysis

The total number of participants recruited for the study was 79. The sample size was selected to allow an estimate of uptake within $\pm 6.6\%$ of the target uptake of 10% [55] with 95% confidence while allowing the research team to obtain sufficient data on the feasibility and potential efficacy of the ILED and CLED.

This study will not undertake significance tests of changes to the primary outcome measures. Descriptive, graphical (summary), and basic inferential statistics of outcomes will be presented as appropriate, for example, frequencies and percentages, mean and SD, or median and quartiles. Confidence intervals (95%) will be calculated to show the change from baseline in the outcomes for each group.

Questionnaires used as outcome measures are quantitative and will be analyzed using appropriate descriptive statistics as per standard.

Changes to diabetes medication will be presented using the medication effect score (MES). The MES for a participant is the sum of the MES for each of their individual medications, where $MES = \text{actual drug dose} / \text{maximum drug dose} \times \text{drug mean adjustment factor}$. A decrease in MES corresponds to a decrease in the use of diabetes medications [56]. Changes to BP medications will be presented using a Treatment Intensity Score (TIS) defined as the actual drug dose/maximum drug dose [57]. The TIS for a participant is the sum of the TIS for each of their medications, and a decrease in TIS indicates a decrease in BP medications.

An ITT analysis using multiple imputations will be conducted for percentage weight loss, HbA_{1c}, and MES. All other outcomes will be presented only for those who completed the trial.

Data Management

Data were recorded on hard copy case report forms and subsequently transferred to a database with ranges and programmed validation checks to aid reliable data entry. Data are held on secure servers at MFT.

Trial Steering Committee and Trial Management Group

The trial steering committee provided oversight for participant safety and included 2 co-principal investigators (BI and MH), an external endocrinologist and independent external advisor with experience of LEDs in the management of T2D. The committee met every 3 months to review and ensure the safety aspects of the trial. The trial management group, which comprised the chief investigators, diabetes specialist dietitians, a diabetes specialist nurse, and research nurses, evaluated all adverse events. The trial could have been stopped by the sponsor, chief investigators, or the trial management group or trial steering committee on the basis of new safety information or for other reasons given by the research ethics committee, but this was not required. The trial was subject to inspection and audit by MFT as the trial sponsor.

Results

The project was funded in May 2017, ethical approval was obtained in August 2017, and enrollment began in February 2018. In total, 79 participants were recruited and randomized to the ILED (n=39) and CLED (n=40) arms of the trial. Data collection was completed in February 2020. Data analysis began in June 2020, and the first results are expected to be submitted for publication in 2021.

Discussion

This is the first study to compare an ILED with an isocaloric CLED to achieve and maintain weight loss and normoglycemia among patients with T2D and overweight and obesity. The study will inform the acceptability and potential efficacy of high-frequency remote follow-up in patients with T2D and overweight and obesity undertaking low energy diets. It will also contribute to the limited data on the safety and efficacy of patients with T2D on insulin undertaking a ILED or CLED. The study did not have a standard or best practice control group for comparison and was not powered to show statistical differences between the groups. However, the planned quantitative and qualitative analyses will assess the feasibility of the programs and inform the case for a future definitive trial.

Acknowledgments

This work was supported by Nestlé Health Science and Oviva UK Limited. Oviva also contributed to the study design. There are no restrictions on the publication of the results of this study, and the contract between the funder and the sponsor (MFT, Research and Innovation, Wythenshawe Hospital, M23 9LT) ensures that the funding body will have no say in the decisions regarding publication. The authors would like to thank Bowland Medical Practice, Northenden Group Practice, and Washway Road Medical Centre for their role in recruitment; John Belcher for his invaluable advice on the statistics; Lucinda Summers for her role as an external endocrinologist overseeing the safety of the study; and Cathy Spence, Schvearn Allen, and the wider MFT Research and Innovation team for their contributions to the set-up and conduct of the trial. The MIDDAS team also thank the participants for their valuable contribution to the study and without whom research of this kind would not be possible.

Authors' Contributions

MH, BI, and SM designed the study and secured the funding. SM drafted the manuscript for publication with input from MH and BI. All other authors have proofread and checked the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest. Nestlé Health Science, as the funder of the trial, is also the manufacturer of the nutritional products used in the trial. Oviva provided a smartphone app used in the trial.

Multimedia Appendix 1

Monitoring and medication management plan.

[[DOCX File, 28 KB - resprot_v10i3e21116_app1.docx](#)]

Multimedia Appendix 2

Support provided by the multidisciplinary team.

[[DOCX File, 21 KB - resprot_v10i3e21116_app2.docx](#)]

Multimedia Appendix 3

Binge Eating Scale.

[[DOCX File, 32 KB - resprot_v10i3e21116_app3.docx](#)]

Multimedia Appendix 4

Weight efficacy lifestyle questionnaire short-form.

[\[DOC File , 49 KB - resprot_v10i3e21116_app4.doc \]](#)

Multimedia Appendix 5

Generalized anxiety disorder scale.

[\[DOCX File , 119 KB - resprot_v10i3e21116_app5.docx \]](#)

Multimedia Appendix 6

Patient health questionnaire.

[\[DOCX File , 124 KB - resprot_v10i3e21116_app6.docx \]](#)

Multimedia Appendix 7

Alcohol use disorders identification test.

[\[DOC File , 128 KB - resprot_v10i3e21116_app7.doc \]](#)

Multimedia Appendix 8

Physical activity readiness questionnaire.

[\[DOCX File , 49 KB - resprot_v10i3e21116_app8.docx \]](#)

Multimedia Appendix 9

Mediterranean diet score.

[\[DOCX File , 31 KB - resprot_v10i3e21116_app9.docx \]](#)

Multimedia Appendix 10

Scottish physical activity questionnaire.

[\[DOC File , 97 KB - resprot_v10i3e21116_app10.doc \]](#)

Multimedia Appendix 11

Eq-5d-3l.

[\[DOCX File , 63 KB - resprot_v10i3e21116_app11.docx \]](#)**References**

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Abbreviations

ADDQoL: Audit of Diabetes-Dependent Quality of Life
AUDIT: Alcohol Use Disorders Identification Test
BES: Binge Eating Scale
BP: blood pressure
CLED: continuous low-energy diet
DiRECT: Diabetes Remission Clinical Trial
GAD: Generalized Anxiety Disorder
GP: general practitioner
HbA_{1c}: glycated hemoglobin
HCP: health care professional
ILED: intermittent low-energy diet
IMD: Index of Multiple Deprivation
ITT: intention-to-treat
LED: low-energy diet
MES: medication effect score
MFT: Manchester University NHS Foundation Trust
MIDDAS: Manchester Intermittent versus Daily diet Diabetes App Study
NHS: National Health Service
PA: physical activity
PAR-Q: Physical Activity Readiness Questionnaire
PHQ-9: Patient Health Questionnaire-9
RCT: randomized controlled trial
T2D: type 2 diabetes
TIS: Treatment Intensity Score
WEL-SF: Weight Efficacy Lifestyle Questionnaire Short Form

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Protocol

The Impact of Enhanced Recovery After Surgery on Total Joint Arthroplasty: Protocol for a Systematic Review and Meta-analysis

Siddharth Rele^{1,2}, BBiomedSc; Cade Shadbolt¹, BA, MA; Chris Schilling¹, BEng (Hons), BCom (Hons), MSc, PhD; Nicholas F Taylor^{3,4}, BAppSc, PhD; Michelle M Dowsey^{1,5}, BHealthSci, MEpi, PhD; Peter F M Choong^{1,5}, MBBS, MD

¹Department of Surgery, St Vincent's Hospital, University of Melbourne, Melbourne, Australia

²Melbourne Medical School, University of Melbourne, Melbourne, Australia

³College of Science, Health and Engineering, La Trobe University, Melbourne, Australia

⁴Allied Health Clinical Research Office, Eastern Health, Melbourne, Australia

⁵Department of Orthopaedics, St Vincent's Hospital, Melbourne, Australia

Corresponding Author:

Siddharth Rele, BBiomedSc

Department of Surgery

St Vincent's Hospital

University of Melbourne

Level 2, Clinical Sciences Building

29 Reagent Street

Melbourne, 3065

Australia

Phone: 61 390355511

Email: srele@student.unimelb.edu.au

Abstract

Background: The number of total joint arthroplasties (TJAs) being performed is increasing worldwide. To match this increasing demand, there has been focus on hastening patients' recovery of function. This effort has culminated in the formulation of enhanced recovery after surgery (ERAS) strategies. However, with evolving ERAS programs and new recommendations, a review of current evidence is required to provide clinicians with up-to-date information about its effect on outcomes for TJA.

Objective: The objective of this study is to assess the utility of ERAS programs on patient, health service, and economic outcomes for primary, elective total hip arthroplasty (THA) and total knee arthroplasty (TKA).

Methods: A systematic search will be conducted in Medline (Ovid), EMCARE (Ovid), EMBASE (Ovid), Web of Science, CINAHL, National Health Service Economic Evaluations Database, and the Cochrane Library. Analytical, observational, and experimental designs will be included in this systematic review. Only studies including patients undergoing primary TKA and THA comparing ERAS programs with conventional surgery and postoperative care will be included. Data related to patient outcomes, health service outcomes, safety, and economic evaluation will be extracted.

Results: The search terms and primary database searches have been finalized. Findings will be reported in narrative and tabular form. Where appropriate, random effects meta-analyses will be conducted for each outcome, and heterogeneity quantified with Cochran Q test and I² statistic. Measures of effect or mean differences will be reported with 95% confidence intervals. The results of this systematic review will be disseminated in a peer-reviewed journal.

Conclusions: This protocol will guide a systematic review assessing outcomes associated with ERAS surgery in primary THA and TKA.

Trial Registration: Open Science Framework osf.io/y4bhs; <https://osf.io/y4bhs>

International Registered Report Identifier (IRRID): PRR1-10.2196/25581

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KEYWORDS

enhanced recovery after surgery; total knee arthroplasty; total hip arthroplasty; systematic review; meta-analysis; postoperative outcomes; economic evaluation

Introduction

The number of total joint arthroplasty (TJA) performed worldwide is increasing [1-4]. In the United States alone, the number of total hip (THA) and total knee (TKA) arthroplasties performed each year has doubled between 2000 and 2014 [5]. With this increasing demand, reducing length of stay (LOS) has become a focus as a key hospital performance indicator [6] and a method of containing procedure-level costs [7]. Decreasing LOS for TJA [8,9] has also made way for the introduction of a strategy for outpatient surgeries [10].

Despite the importance of limiting unnecessary time in hospital following TJA, it is vital that strategies that aim to decrease LOS do not come at the expense of patients experiencing inferior postoperative outcomes. Enhanced recovery after surgery (ERAS) offers one promising approach to reducing LOS by streamlining preoperative and perioperative care [11,12]. These principles were first promulgated by Kehlet et al [13] for colorectal surgery more than 20 years ago. More recently, growing attention has been paid to whether the principles of ERAS can be employed to reduce LOS following TJA. Despite this, prior to 2020, there were no consensus statements regarding the implementation of ERAS principles in the context of arthroplasty. Since then, the ERAS society, the body responsible for proposing recommendations for ERAS protocols in surgery, has released recommendations for perioperative care after arthroplasty [14,15]. However, the proposed ERAS items highlighted in these recommendations stand in contrast to those currently published in literature—namely with the use of peripheral nerve blocks and postoperative analgesia [16].

Evidence relating to the safety and efficacy of implementing ERAS pathways is fast evolving. Recent systematic reviews by Zhu et al [11] and Deng et al [12] found ERAS programs reduced both LOS and incidence of complications in the 30 days following THA and TKA, without driving a commensurate increase in re-admission following discharge. In addition, one previous review on the cost-effectiveness of ERAS pathways found ERAS surgery to be dominant compared with conventional treatment [17]. To date, available systematic reviews have yet to explore the evidence relating to other post-acute care outcomes such as emergency department visits, postoperative primary care visits, and revision surgery. Moreover, these systematic reviews have reported only total complications and re-admissions in the 30 days following surgery, and neglected to examine outcomes over a longer period or to stratify the analysis by medical and surgical complications and re-admissions [18,19]. Furthermore, previous cost analyses have been based on small number of studies with fewer than 50 patients in each treatment arm [20,21]. Finally, the previously published systematic reviews have not assessed the impact of the number of type of items that may be combined as part of a particular ERAS program. Rather, they have focused only on comparing cohorts undergoing surgery informed by ERAS principles and those without [11,12,17].

Collectively, the limited scope of prior systematic reviews leaves us without a comprehensive picture of the potential risks associated with ERAS pathways—and with an incomplete understanding of the necessary features of a safe and effective ERAS pathway for patients undergoing arthroplasty. With these considerations in mind, the proposed systematic review and meta-analysis aims to assess the utility of ERAS programs on patient, health service, and economic outcomes for primary, elective THA, and TKA.

Methods**Study Reporting and Registration**

This systematic review protocol will be reported according to the “Preferred Reporting Items for Systematic Review and Meta-analysis – Protocols” (PRISMA-P) [22] and the “Meta-Analysis of Observational Studies in Epidemiology” (MOOSE) [23] guidelines. In addition, this review has been registered prospectively with Open Science Framework. Any conflict between reviewers throughout the review process will be resolved through discussion; and if a consensus is not able to be reached, a third author will be consulted. The full search strategy for the primary databases can be found in [Multimedia Appendix 1](#).

Criteria for Inclusion**Type of Studies**

All analytical, observational, and experimental studies will be included in this systematic review. Studies that will be excluded are descriptive studies, case reports, editorials, commentaries, qualitative studies, and literature reviews. Reference lists of relevant systematic and literature reviews will be searched to find additional studies that can be included. Only studies written in English will be included.

Type of Population

The population of interest is patients undergoing primary, elective THA or TKA. Studies will also be included if patients are undergoing bilateral procedures (including simultaneous and sequential procedures), as these procedure types may determine discharge destination.

Patients undergoing revision or partial arthroplasty and those undergoing arthroplasty for fractures will be excluded. Studies involving a mixed cohort will be included provided that sufficient data are present on measures of primary, elective TJA.

Type of Intervention

For the purposes of this review, ERAS programs will include fast-track surgery. The intervention of interest is any type of ERAS recovery program, which includes more than 1 item that is distinct from the conventional treatment program. Examples of such items include use of preoperative patient education, standardized anesthetic technique, and early and intensive mobilization.

Type of Comparator

The comparator of interest is conventional surgery and postsurgical pathway.

Outcomes of Interest

Primary Outcomes

These are centered around outcomes of arthroplasty and include patient outcomes, health service outcomes, and safety.

Patient Outcomes

Any measures of patient-reported outcome measures (eg, pain, function, global assessment, health-related quality of life) will be recorded. These will be stratified according to the timeframes examined (eg, 6 months, 1 year) up to 2 years postoperatively. In addition, measures of mobility, including, but not limited to, 6-minute walk test and walking speeding will be assessed.

Health Service Outcomes

These include LOS, discharge destination, duration of rehabilitation, primary care visits and emergency department visits, and re-admissions within 90 days of surgery. Re-admission will be categorized into medical and surgical causes, if possible [18]. Discharge destinations will be grouped into inpatient rehabilitation and discharge home; sensitivity analyses will be utilized to assess the impact of differing levels of postdischarge support, such as home with support, home without support.

Safety

This includes data on patient safety, including mortality, and any complications. All will be reported for 30 and 90 days. Complications will be grouped and organized into type of complication (eg, medical or surgical complication [18]). In addition, complications tied directly to the procedure, including surgical site infections, stiffness, manipulations under anesthesia, and revision surgery, will have no time restrictions placed.

Secondary Outcomes

These outcomes are centered around economic evaluation (any measure including, but not limited to, measures of cost-effectiveness, cost savings, total cost).

Search Strategy

To ensure that a Cochrane review has not been published on the topic of impact of reducing LOS on post-acute care, the Cochrane library has been searched using the MeSH term and keyword “Arthroplasty.” This search has confirmed a Cochrane review has not been previously published on this topic.

Database searches were devised with recommendations from an external research librarian and previous literature suggesting optimal database combinations [24]. A comprehensive literature search will be performed of MEDLINE (Ovid), Web of Science, CINAHL, Emcare (Ovid), Embase (Ovid), National Health Service Economic Evaluations Database, and the Cochrane library from their inception to January 2021. In addition, Google scholar will be utilized to supplement the primary database search and reduce the risk of publication bias. Keywords and MeSH were combined with the operator “OR” for the population

and intervention. The population and intervention queries were combined with the “AND” operator.

Study Selection

Following independent screening of the first 10% of studies, the agreed eligibility criteria will be refined by discussion between the 2 reviewers (SR and CSh), as per PRISMA-P guidelines [22]. This final eligibility criteria will then be utilized to independently screen titles and abstract of identified citations by 2 reviewers. Any arising discrepancies will be resolved through discussion between reviewers.

Forward and backward citation tracking of studies for full-text screening will be used to identify any additional studies. Following this, the same 2 reviewers will undertake screening of full-text studies to determine final eligibility for inclusion. A PRISMA flow diagram will be used to report the findings of this study selection process [25]. A further full-text review will be undertaken of potentially eligible studies. Interrater reliability will be assessed and will be reported as Cohen kappa statistic [26] to inform the agreement between reviewers.

Given that retrospective studies may report on the same population within the same timeframe, care will be taken to determine if these studies are independent. In the event that multiple studies are determined to be assessing the same population, all of these studies will be treated as one, and reference to all will be made, to reduce the risk of overestimation [27]. A further critical analysis of these studies will be undertaken to highlight any discrepancies, and authors will be contacted if such discrepancies are identified.

Data Collection and Management

The first round of deduplication will be undertaken through EndNote X9. After this, Covidence will be used to perform further deduplication, screening, and data extraction. STATA (version 16) software will be used to conduct statistical analyses.

Two reviewers will use a standardized data extraction form to extract data from each study independently. A further comparison of this, completed, data extraction form to assess consistency and accuracy will also be undertaken. Inconsistencies will be resolved with discussion with other authors. Study authors will be contacted via email if full-text copies of included studies are unattainable or clarification of methods or results is required.

The form for data extraction will follow items 1 to 16 in the “Reporting on ERAS Compliance, Outcomes, and Elements Research (RECOVER)” checklist [28] to inform details of the article, characteristics of patients and the details of the enhanced recovery program, and compliance within the program. The details of the employed enhanced recovery strategies will also be scored against the ERAS society’s recommendation.

In addition, a results summary will be recorded with total number of patients and total number of patients with outcomes; any measure of prognostic effect (including odds ratio, relative risk and hazard ratios); standardized mean difference or mean difference and 95% confidence intervals for each outcome measure as appropriate; use of univariate/multivariate analysis; and variables included in multivariate analysis. Patient-reported

outcome measures will be recorded in means (SD), and any measure of economic evaluation will be recorded.

Data extraction for health economic outcomes will additionally include the following:

- Economic evaluations: economic study design, comparators, time horizon analyzed, use of discounting.
- Models: model type, model structure, assumptions, source of data (baseline and outcome of interest), model uncertainty, method of internal/external validation.
- All: costs included, source of cost data, source of utility data, quality of life instruments used, study results (currency, cost year, incremental cost effectiveness ratio).

Any missing values will be calculated provided sufficient data are available. Study authors will be contacted to obtain missing data.

Risk of Bias Assessment

Risk of bias will be assessed by 2 reviewers through the Cochrane Risk-of-Bias 2 (RoB 2) tool [29] for randomized trials and Newcastle-Ottawa Scale (NOS) [30] for nonrandomized studies. Health economic outcomes will be assessed with the Consensus on Health Economic Criteria (CHEC) list [31], and model-based studies with the questionnaire produced by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) [32]. A summary table presenting all articles included in the review will be used to present the results of the critical appraisal. Meta-analysis will be performed if articles have adequate data for quantitative synthesis, and those with a high risk of bias will be excluded in the form of a sensitivity analysis to determine their influence on the meta-analysis [33].

Data Synthesis and Statistical Analysis

All studies will be presented in both tabular and narrative form. A quantitative analysis of the findings from the included studies is planned for all outcomes. A random effects model will be utilized as heterogeneity is anticipated between studies [34]. Meta-analyses will be reported with a measure of effect (for dichotomous outcomes) and mean difference (for continuous outcomes). When different outcome measures are utilized for the same outcome, a standardized mean difference will be reported [35]. 95% confidence intervals will be reported for all. Care will be taken to report continuous variables separately from categorical variables.

Heterogeneity will be assessed by the Cochran Q test and I^2 statistic [36]. Subgroup analyses with random-effects meta-analysis will be undertaken when significant heterogeneity is encountered. If heterogeneity is not resolved through this process, exclusion of any outlying studies in the form of sensitivity analysis will be considered if a clear explanation for conflicting results is found upon review of the papers in question. Results of meta-analysis, both including and excluding papers in question, will be presented and interpreted. If variation in the results cannot be accounted for, a meta-analysis will not be conducted, and results will be presented as per the “Synthesis Without Meta-analysis” (SWiM) guidelines [37]. Pooled estimates will be reported with a forest plot and 95% confidence interval.

Several subgroup analyses are planned if data permits. Studies will be grouped according to their ERAS protocol to understand the impact of different ERAS programs on outcomes. Additionally, each ERAS protocol will be scored according to the number of ERAS society recommendations implemented to understand the cumulative impact of the ERAS recommendations [14, 15]. The impact of varying levels of compliance within ERAS programs will also be evaluated through a subgroup analysis. A separate subgroup analysis for programs using a same-day discharge or outpatient surgery will also be conducted. Finally, the impact of patient-related factors, within ERAS surgery, on outcomes will also be explored.

Furthermore, it is also possible that a single comparator may not be determinable, as a significant portion of the included studies may present LOS as a continuous variable. As such, analyses will be undertaken with LOS as a continuous and categorical variable (categories for LOS will be formulated depending on the included studies). If significant differences in specific components of ERAS programs, such as the composition of spinal anesthesia, method of preoperative education, or duration of postoperative regional analgesia, are encountered between studies, sensitivity analyses will be used to assess the impact of these differences.

Publication Bias

Strategies employed to reduce risk of publication bias include a search strategy that does not restrict gray literature, and data from unpublished work included in meta-analysis [33,38]. Furthermore, nonreporting biases will be attempted to be identified from other factors through contour-enhanced funnel plots with an appropriate test of asymmetry for meta-analyses including at least ten studies [38,39]. Any potential sources of asymmetry will be explored; and a trim and fill method will be utilized to account for the possibility of publication bias if deemed appropriate [40].

In addition, outcomes mentioned in the “Methods” section of studies will be compared with those in the results during the data extraction process. In randomized trials, the final reported outcomes will be compared with a published protocol, if available. Both reviewers will assess the completed data extraction table to determine whether certain outcomes were included by most included studies but not addressed by a few. If reporting bias is found, studies will be investigated for possible explanations, and authors may be contacted to provide clarity [33].

Confidence in Cumulative Evidence

The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach will be used by 2 reviewers, to independently assess the quality of cumulative evidence [41,42]. The quality of evidence will be downgraded if significant limitations are present, as evidenced from the risk of bias. In addition, evidence will be downgraded if wide confidence intervals are encountered and if statistical heterogeneity, as assessed through the I^2 statistic, is over 25% [43].

Results

A preliminary search of the primary databases has been conducted. The final database search was conducted in January 2021. This search will also be repeated prior to final publication of results. We plan on disseminating the findings of this systematic review in a peer-reviewed journal.

Discussion

The primary focus of previous systematic reviews published on ERAS principles have relied upon authors to propose their own

definitions of ERAS surgery. With the publication of the ERAS Society's new recommendations, having objective criteria to assess these ERAS protocols allows the effects of ERAS principles to be examined with greater clarity. The results of this systematic review will help to aggregate current research and provide greater insight into the risks and benefits of reducing LOS for TJA. In addition, this review will also aid policy makers to better understand whether reductions in LOS through ERAS pathways are occurring to the detriment of the patient and health system more broadly.

Authors' Contributions

SR drafted the manuscript. SR, CSh, CSc, NT, MD, and PC contributed to the design of the review protocol. All authors approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Search strategies for primary databases.

[[DOCX File , 19 KB - resprot_v10i3e25581_app1.docx](#)]

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Abbreviations

CHEC: Consensus on Health Economic Criteria

ERAS: enhanced recovery after surgery

ISPOR: International Society for Pharmacoeconomics and Outcomes Research

LOS: length of stay

MOOSE: Meta-Analysis of Observational Studies in Epidemiology

NOS: Newcastle-Ottawa Scale

PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-analysis – Protocols

RECOvER: Reporting on ERAS Compliance, Outcomes, and Elements Research

THA: total hip arthroplasty

TJA: total joint arthroplasty

TKA: total knee arthroplasty

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Protocol

Mobile Health Crowdsensing (MHCS) Intervention on Chronic Disease Awareness: Protocol for a Systematic Review

Temitope Oluwaseyi Tokosi^{1*}, BCom, MA, PhD; Michael Twum-Darko^{1*}, BSc, MCom, PhD

Graduate Centre for Management, Faculty of Business and Management Sciences, Cape Peninsula University of Technology, Cape Town, South Africa

*all authors contributed equally

Corresponding Author:

Temitope Oluwaseyi Tokosi, BCom, MA, PhD
Graduate Centre for Management
Faculty of Business and Management Sciences
Cape Peninsula University of Technology
Keizersgracht Street
District Six Campus
Cape Town, 8000
South Africa
Phone: 27 76 047 1328
Email: toksymoore@gmail.com

Abstract

Background: Mobile health crowdsensing (MHCS) involves the use of mobile communication technologies to promote health by supporting health care practices (eg, health data collection, delivery of health care information, or patient observation and provision of care). MHCS technologies (eg, smartphones) have sensory capabilities, such as GPS, voice, light, and camera, to collect, analyze, and share user-centered data (explicit and implicit). The current literature indicates no scientific study related to MHCS interventions for chronic diseases. The proposed systematic review will examine the impact of MHCS interventions on chronic disease awareness.

Objective: The objectives of this study are to identify and describe various MHCS intervention strategies applied to chronic disease awareness.

Methods: Literature from various databases, such as MEDLINE, Embase, PsycINFO, CINAHL, and Cochrane Central Register of Controlled Trials, will be examined. Trial registers, reports, grey literature, and unpublished academic theses will also be included. All mobile technologies, such as cell phones, personal digital assistants, and tablets that have short message service, multimedia message service, video, and audio capabilities, will be included. MHCS will be the primary intervention strategy. The search strategy will include keywords such as *mHealth*, *crowdsensing*, and *awareness* among other medical subject heading terms. Articles published from January 1, 1945, to December 31, 2019, will be eligible for inclusion. The authors will independently screen and select studies, extract data, and assess the risk of bias, with discrepancies resolved by an independent party not involved in the study. The authors will assess statistical heterogeneity by examining the types of participants, interventions, study designs, and outcomes in each study, and pool studies judged to be statistically homogeneous. In the assessment of heterogeneity, a sensitivity analysis will be considered to explore statistical heterogeneity. Statistical heterogeneity will be investigated using the chi-square test of homogeneity on Cochrane Q test, and quantified using the I^2 statistic.

Results: The preliminary search query found 1 paper. Further literature search commenced in mid-March 2021 and is to be concluded in April 2021. The proposed systematic review protocol has been registered in PROSPERO (The International Prospective Register of Systematic Reviews; no. CRD42020161435). Furthermore, the use of search data extraction and capturing in Review Manager version 5.3 (Cochrane) commenced in January 2021 and ended in February 2021. Further literature search will begin in mid-March 2021 and will be concluded in April 2021. The final stages will include analyses and writing, which are anticipated to start and be completed in May 2021.

Conclusions: The knowledge derived from this study will inform health care stakeholders—including researchers, policy makers, investors, health professionals, technologists, and engineers—of the impact of MHCS interventions on chronic disease awareness.

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KEYWORDS

mHealth; crowdsensing; chronic diseases; awareness; mobile phone

Introduction

Mobile health (mHealth) is a component of eHealth that involves the use of mobile communication technologies to promote health by supporting health care practices (eg, health data collection, health care information delivery, or provision of care and patient observation) [1]. Crowdsensing is a paradigm, which, as advocated by Banda [2], is based on the crowdsourcing concept of engaging a crowd to solve a complex problem through an open forum. The term *mobile* in *mobile crowdsensing* means using mobile smart devices, such as smartphones, and involving human mobility when using these devices [3]. mHealth crowdsensing (MHCS), on the other hand, takes advantage of pervasive mobile smart devices to efficiently collect data, enabling numerous large-scale applications [4]. It is made possible through human involvement, which is an important key feature.

Similarly, MHCS applications have been reported in studies by Pryss et al [5], who investigated a MHCS platform, Track Your Tinnitus. This platform uses smart mobile devices, a website, a backend system, and 2 mobile applications for patients over a 12-month period. Similarly, Giannotta [6] undertook research to design an MHCS application called Track your Diabetes. In the study by Bellavista et al [7], an MHCS-based middleware known as Collaborative Emergency Group Assistant (COLLEGA) was shown to enhance the potential of supporting participatory management of mHealth communities for emergency scenarios. Furthermore, the study of Reddy et al. [8] described DietSense, a software system that supports people who want to lose weight. At last, the study of Gao et al [9] involved designing a novel health-aware smartphone system, HealthAware, which uses an embedded accelerometer to monitor daily physical activities and a built-in camera to analyze food items.

The mobile devices or technologies applied to health include mobile phones, such as smartphones, tablets, portable media players, and their mHealth apps [10]. Smartphones, having sensory capabilities, such as GPS, voice, light, and camera, are the devices most suitable for MHCS research, as they have the ability to collect, analyze, and share user-centered data (explicit and implicit) [11].

Understanding chronic disease follows Goodman et al's [12] argument that there is no single uniform definition. For this paper, the authors combine and adopt the Centers for Disease Control and Prevention (CDC) [13] and Health and Human Services (HHS) [14] definitions, with the former defining chronic diseases as "conditions that last 1 year or more and require ongoing medical attention or limit activities of daily living or both" [13].

Chronic diseases are synonymous with infectious diseases. Tokosi et al [3] undertook a scoping review on MHCS applied to chronic diseases, including arthritis, asthma, cancer, diabetes,

HIV, obesity, sclerosis, and tinnitus. COVID-19 does not fit the definition of a chronic disease for this study.

Some research cases highlighting MHCS intervention for chronic diseases are presented here. For example, the study by Edoh [15] showcased a proof of concept in the prevention of the spread of emerging infectious diseases using a hybrid crowdsensing paradigm. The study revealed positive results, such as a potential to improve conventional epidemiological data collection. Pryss et al's [5] study highlights MHCS intervention for the chronic disease tinnitus through awareness, diagnosis, and potential treatment; meanwhile, their study on mobile crowdsensing services for tinnitus assessment and patient feedback revealed that mobile feedback service can assist patients in demystifying tinnitus and taking control of it, which should facilitate them to better cope with the condition [16].

The objectives of this study are to identify and describe the various MHCS intervention strategies used for chronic diseases and to assess their impact on chronic disease awareness. A motivation for this study is that MHCS technology has rarely been used in clinical contexts [17].

Methods

This manuscript adheres to the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) 2015 checklist ([Multimedia Appendix 1](#)) in line with a submission for systematic review protocols [18]. This protocol has been registered with PROSPERO (the International Database of Prospective Register of Systematic Reviews; no. CRD42020161435) [19].

Study Design

This review will include randomized and nonrandomized studies. For nonrandomized studies, case-control, cohort, and cross-sectional studies in which MHCS was the main primary intervention strategy used for chronic disease awareness will be included. Studies in which MHCS was used as an intervention strategy for chronic disease screening will also be included.

Study Participants

Study participants will be both female and male, and no age restriction will be applied. Individuals of any race, ethnicity, employment status, occupation, and geographical location will be eligible for inclusion.

Types of Interventions

The relevant MHCS interventions for this study focus primarily on positively impacting chronic diseases awareness. MHCS interventions for health care consumers vary. For example, in the study by Pryss et al [16], MHCS was designed to provide patients with aggregated information about the variation of their tinnitus over time. This is a form of health awareness strategy where the mobile feedback service helps a patient to understand, get better control of, and cope with their chronic health

condition. Meanwhile, the Free et al's [20] strategy categorizes by device (eg, mobile phone, personal digital assistant [PDA]) and modality (eg, SMS, text messaging, multimedia message service [MMS], video). This will be used in describing the interventions [20].

Types of Technology

Mobile devices having sensory capabilities, such as GPS, camera, and light, is a typical feature of the technology used for MHCS. Also, cellular communication that allows for wireless and 3G/4G capabilities will be part of the study. These devices include mobile phones (including Android and IOS smartphones), PDAs and PDA phones, tablets, smartphone apps, ultraportable computers, and smart books [10,21].

MHCS smartphone functionalities comprise voice over internet protocol, SMS, text messaging, MMS, GPS, Bluetooth, audio, email, light sensing, and internet [22]. Some applications using MHCS modalities include data collection (web) [23,24], patient health education (web) [6], patient health self-management (text) [25,26], behaviour change communication (images, audio, text) [27], sensors and point-of-care devices (camera, microphone, GPS, accelerometer, digital compass, Bluetooth sensing) [28], provider communication (SMS, MMS, smartphone camera), provider training and education (SMS, MMS, audio, video), human resource management (voice, SMS), supply chain management (GPS, SMS), and financial transactions and incentives (mobile banking service, airtime transfers) [10,17,29].

Outcomes

The proposed MHCS intervention impact on chronic disease awareness will be reviewed by assessing the following: the increased attendance at clinics for chronic diseases; the stage of chronic diseases when diagnosed (as this will assist in determining whether MHCS has promoted early detection and screening); and increased chronic disease inquiry via call centres, online forums, and social media. User acceptability will not be assessed as an outcome.

Chronic disease awareness is described as the ability to be fully informed and knowledgeable of a terminal disease suffered by a patient [30]. Furthermore, where actual patient numbers cannot be determined, the baseline for assessment will be determined by the keywords *increase*, *improvement*, or *rise* used in the study.

Study Setting

Geographical setting will not be restrictive in the study. All available health facilities where MHCS research on chronic diseases were conducted will be included. This approach allows for all relevant information sources to be captured.

Exclusion Criteria

Study types will be excluded according to the following criteria described by Tokosi et al [25]: non-English language papers; studies before January 1, 1999, and after December 31, 2019; nonhealth-related studies; letters, commentaries, and editorials; studies lacking primary data or explicit method description; duplicate studies that are published in more than one journal or report (the most comprehensive and up-to-date version will be used); studies not including human involvement; and studies not having a health-technology application focus.

Search Strategy

Banda [2] highlights the origins of crowdsourcing that date back to the 19th century when Joseph Henry created the first national weather map of the United States in 1856 using a new networked technology of his day (the telegraph) to crowdsource weather reports from across the country [31]. In our study, the earliest start date will be when each database began operation. All major databases, including MEDLINE, Embase, PsycINFO, CINAHL, The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register), National Health Services Health Technology Assessment Database, Scopus, Web of Science, and Google Scholar, will be included [30]. The language of publication will be limited to English for reasonable analysis purposes.

Other Sources

The phrase *chronic disease* will be used to expand the search strategy (where necessary), which will include grey literature and other databases, including SpringerLink, Wiley InterScience, trial registers, Institute of Electrical and Electronics Engineers, Association for Computing Machinery Digital Library, and CiteSeer [29]. We concur with the experimental findings proposed by Fortuin et al [10] in identifying accurate search terms in the development of an optimum search strategy. For trial registers, we will identify ongoing studies and recently completed trials. The studies to be included will be selected using predefined search terms adapted for the databases to be used. Full-text articles of studies extracted from reference lists will be reviewed. Manual searches of reference lists of primary studies, and of relevant and previously published reviews will be completed. Grey literature will comprise unpublished studies identified in universities and other institutional repositories, with the same eligibility criteria applied. The MEDLINE format for searching key terms is detailed in Table 1 and in Multimedia Appendix 2. The number of identified references following a preliminary search is reported in Table 1.

Table 1. Preliminary search query classification.

Number	Query ^a	Results, n
1	Search: (((((((((((mhealth) OR (telemedicine)) OR (wireless technology)) OR (mobile phone)) OR (smartphone)) OR (cellphone)) OR (mobile technology)) OR (mobile device)) OR (mobile-based phone)) OR (tablet computer)) OR (IPAD)) OR (pda)) OR (mhealth application)	102,787
2	Search: (((((((((((mhealth) OR (telemedicine)) OR (wireless technology)) OR (mobile phone)) OR (smartphone)) OR (cell phone)) OR (mobile technology)) OR (mobile device)) OR (mobile-based phone)) OR (tablet computer)) OR (IPAD)) OR (pda)) OR (mhealth application)) AND (crowdsourcing)	162
3	Search: (((((((((((mhealth) OR (telemedicine)) OR (wireless technology)) OR (mobile phone)) OR (smartphone)) OR (cell phone)) OR (mobile technology)) OR (mobile device)) OR (mobile-based phone)) OR (tablet computer)) OR (IPAD)) OR (pda)) OR (mhealth application))) AND (crowdsensing)	33
4	Search: (((((((((((mhealth) OR (telemedicine)) OR (wireless technology)) OR (mobile phone)) OR (smartphone)) OR (cellphone)) OR (mobile technology)) OR (mobile device)) OR (mobile-based phone)) OR (tablet computer)) OR (IPAD)) OR (pda)) OR (mhealth application))) AND (crowdsensing)) AND (disease)	1

^aFilters include publications from January 1, 1945, to December 31, 2019.

Study Selection

TT will retrieve all relevant articles from various databases, based on the finalized search strategy. All the literature obtained will be saved in Endnote reference management software (Clarivate Analytics). Both authors will independently screen the titles and abstracts of retrieved studies for eligibility. Both authors will make a final assessment for inclusion using the full-text article. Discrepancies and disagreements will be resolved by both authors.

Data Extraction

A standardized data extraction form adapted from a study by Tokosi et al [30] will be used for data extraction. Full texts of selected abstracts will be retrieved and data extracted in line with the prespecified template. The key information to be extracted includes the following: author name(s) and year of the study, type of participant/study population and demographic characteristics; type of mHealth device used (eg, mobile phones, PDAs, smartphones, tablets); type of intervention (eg, SMS, MMS, video, text, audio); nature of the mHealth intervention (eg, awareness, diagnosis, treatment); type of study (eg, randomized, nonrandomized); type of outcome measured; and findings/results.

Following Saidi et al's [32] procedure, data will be entered into Review Manager software, version 5.3. (Cochrane). Both authors will verify the data entered for missing or incorrect data. If both authors cannot agree on missing data entry, an independent third party will be consulted to mediate. Missing data will be requested from study authors via email [21]. If no response is received from study authors, an attempt will be made to impute missing SD or standard error values using data from other similar studies in the review with similar methods and sample sizes, as recommended by Wiebe et al [33].

Assessing Risk of Bias

The authors will use recommendations by the International Cochrane Collaboration to independently assess the risk of bias [34]. These criteria include randomization sequence generation, treatment allocation concealment, blinding of participants, incomplete outcome data, selective outcome reporting, and other sources of bias [30]. All included studies

will be scored for bias using these criteria. A descriptive summary for each scoring will be recorded. Discrepancies between the review authors regarding the risk of bias in particular studies will be resolved by dialogue, with involvement of an independent third party, where necessary.

Data Analysis and Synthesis

The extracted data will be presented in an evidence table adapted from Saidi et al's [32] study. A descriptive synthesis will be undertaken in accordance with the Centre for Reviews and Dissemination [35]. Continuous outcomes will be ascertained by calculating mean differences and SDs. Ratios and their corresponding 95% CIs will be determined for dichotomous outcomes. Heterogeneity will be used to examine participants, interventions, and outcomes of each study. The statistical test for heterogeneity will include the I^2 test which quantifies heterogeneity; this test will allow for the quality of evidence to be validated [34]. Data will be pooled; where collected data are sufficiently similar, a meta-analysis will be conducted. Similarly, where the variability between studies is high, the results will not be pooled and a narrative synthesis will take place [30]. When appropriate, a subgroup analysis will be used to determine if varying mHealth crowdsensing applications have an impact on chronic disease awareness and in what context this occurs. Subgroups to be considered for this analysis will include age grouping and geographical region.

Various sensitivity analyses as espoused by Tokosi et al [30] will be performed, including analysis conducted based on the study quality (risk of bias and level of participant dropout) to investigate possible sources of heterogeneity. Another analysis will be used to determine how excluded studies could have influenced the overall result. A final analysis to determine how the result would differ from other study results should there be only high-quality studies included will be used [34].

Results

The literature sourcing with regard to the inclusion and exclusion criteria of the study is ongoing. All data to be extracted will be grouped under various headings as specified in the data extraction form, which will include the following: basic study

information (eg, author name, year); type of participant/study population and demographic characteristics; type of mHealth device used (eg, mobile phones, PDAs, smartphones, tablets etc); type of intervention (eg, SMS, MMS, video, text, audio); nature of the mHealth intervention (eg, awareness, diagnosis, treatment); type of study (eg, randomized, nonrandomized); type of outcome measured; and findings/results [30]. The preliminary search query found 1 paper. The literature search will commence in mid-March 2021 and will end in April 2021. It is anticipated that the final review will be completed in May 2021.

Discussion

This review will identify and describe the impact of MHCS interventions on chronic diseases. The findings of the systematic review will inform the design of mHealth interventions for chronic diseases. Furthermore, the study will highlight which mHealth technology modalities (eg, SMS) are appropriate for the target audience when creating awareness for chronic diseases.

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Authors' Contributions

TT conceptualized and drafted the manuscript. MTD reviewed the content of the protocol and edited the manuscript. All authors read and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1

PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) 2015 checklist.

[DOC File, 86 KB - [resprot_v10i3e24589_app1.doc](#)]

Multimedia Appendix 2

Search query.

[DOC File, 27 KB - [resprot_v10i3e24589_app2.doc](#)]

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Abbreviations

CDC: Centers for Disease Control and Prevention

COLLEGA: Collaborative Emergency Group Assistant

HHS: Health and Human Services

MHCS: mobile health crowdsensing

mHealth: mobile health

MMS: multimedia message service

PDA: personal digital assistant

PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols

PROSPERO: The International Prospective Register of Systematic Reviews

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Proposal

Phylogenetic and Mutational Analysis of Lassa Virus Strains Isolated in Nigeria: Proposal for an In Silico Study

Daniel Kolawole¹, BSc; Hayatu Raji¹, PhD, MSc, BSc; Malachy Ifeanyi Okeke¹, PhD, MPhil, BSc

Department of Natural and Environmental Sciences, American University of Nigeria, Yola, Nigeria

Corresponding Author:

Malachy Ifeanyi Okeke, PhD, MPhil, BSc

Department of Natural and Environmental Sciences

American University of Nigeria

Lamido Zubairu Way

Yola,

Nigeria

Phone: 234 8145545022

Email: malachy.okeke@aun.edu.ng

Abstract

Background: In 2018, the total number of Lassa fever cases in Nigeria was significantly higher than that observed in previous years. Hence, studies had attempted to determine the underlying cause. However, reports using phylogenetic methods to analyze this finding ruled out the emergence of potentially more transmissible Lassa virus strains or an increase in human-to-human viral transmission as the cause underlying the increase in cases. Two years later, the situation seems even worse as the number of confirmed cases has reached an all-time high according to situational reports released by the Nigerian Center for Disease Control.

Objective: Considering the increasing trend of Lassa fever cases and related mortality, the major objective of this study is to map mutations within the genomes of Lassa virus isolates from 2018 and 2019 using the reference sequence available at the National Center for Biotechnology Information as a benchmark and compare them to the genomes of viruses isolated during 1969-2017. This study would also attempt to identify a viral marker gene for easier identification and grouping. Finally, the time-scaled evolution of Lassa virus in Nigeria will be reconstructed.

Methods: After collecting the sequence data of Lassa virus isolates, Bayesian phylogenetic trees, a sequence identity matrix, and a single nucleotide polymorphism matrix will be generated using BEAST (version 2.6.2), Base-By-Base, and DIVEIN (a web-based tool for variant calling), respectively.

Results: Mining and alignment of Lassa virus genome sequences have been completed, while mutational analysis and the reconstruction of time-scaled maximum clade credibility trees, congruence tests for inferred segments, and gene phylogeny analysis are ongoing.

Conclusions: The findings of this study would further the current knowledge of the evolutionary history of the Lassa virus in Nigeria and would document the mutations in Nigerian isolates from 1969 to 2019.

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KEYWORDS

Arenavirus; Bayesian phylogeny; epidemic; evolution; Lassa virus; Mammarenavirus; marker gene; molecular epidemiology; mutations; Nigeria

Introduction

Lassa fever, a viral hemorrhagic fever, is caused by Lassa virus. Viral hemorrhagic fevers are a group of viral illnesses that are characterized by damage to the vascular system; hence, they are described as being “hemorrhagic” [1]. Viral hemorrhagic fevers are caused by enveloped RNA viruses from 4 families:

Arenaviridae, Bunyaviridae, Filoviridae, and Flaviviridae [1,2]. The major natural reservoirs of hemorrhagic viruses are usually rodents, fruit bats, and nonhuman primates [3].

Lassa virus is an ambisense RNA virus that belongs to family Arenaviridae and genus *Mammarenavirus*. There are 35 currently recognized viruses within this genus, which are classified into Old World and New World viruses, and Lassa

virus is an Old World virus [4]. The Lassa virus genome contains 2 segments—the L (7.3 kb) and S (3.4 kb) segments—each encoding 2 proteins. The L segment encodes the viral RNA polymerase and zinc-binding proteins, while the S segment encodes the nucleoprotein and glycoprotein precursors [5]. Lassa fever is endemic to various regions of West Africa including Nigeria, Guinea, Sierra Leone, Liberia, Benin, Ghana, Côte d'Ivoire, Togo, and Mali.

Lassa virus is a very diverse group as multiple lineages have been inferred from numerous sequencing projects. The consensus seems to be that Lassa viruses can be categorized into four lineages: I, II, III, and IV. Lineages I, II, and III are endemic to Nigeria, while lineage IV is endemic to Guinea, Sierra Leone, Côte d'Ivoire, Mali, and Liberia [6]. However, other lineages of Lassa virus have been reported across West Africa. Strains V and VI have been proposed after sequencing of strains isolated from Côte d'Ivoire and Mali and from *Hylomyscus pamfi* rodents in Nigeria [7].

Owing to its zoonotic nature, humans can develop Lassa fever upon viral transmission on coming in contact with excreta, urine, or tissue of the reservoirs of the virus. The reservoirs for Lassa virus have been identified to be rodents of genus *Mastomys*, otherwise known as “Multimammate rats” [6,8]. Human-to-human transmission of Lassa virus is also possible most commonly through the nosocomial route when healthy individuals come in direct contact with medical instruments contaminated with Lassa virus or the blood, urine, feces, and other body secretions of a patient with Lassa fever [6,9].

The number of Lassa fever cases was higher in the outbreak in the 2018 transmission season than in previous years in Nigeria [8,10]. Consequently, investigational studies were conducted to address concerns regarding the emergence of a more transmissible Lassa virus strain [8,10]. However, upon genome analysis, it was found that the viruses from the 2018 outbreak clustered with isolates from previous years; therefore, these viruses are believed to originate from the same pool of lineages known to circulate in Nigeria. Furthermore, it was determined that the upsurge in infection rates was not sustained through extensive human-to-human transmission, indicating that the epidemic was fueled by independent zoonotic events, thus dismissing concerns regarding a more transmissible strain [8,10]. Further, unpublished data in 2019 [11-13] are concurrent with the findings of Kafetzopoulou et al [8] in 2018. However, a worsening trend has been observed in subsequent years; with even more Lassa fever cases and related mortalities. Overall,

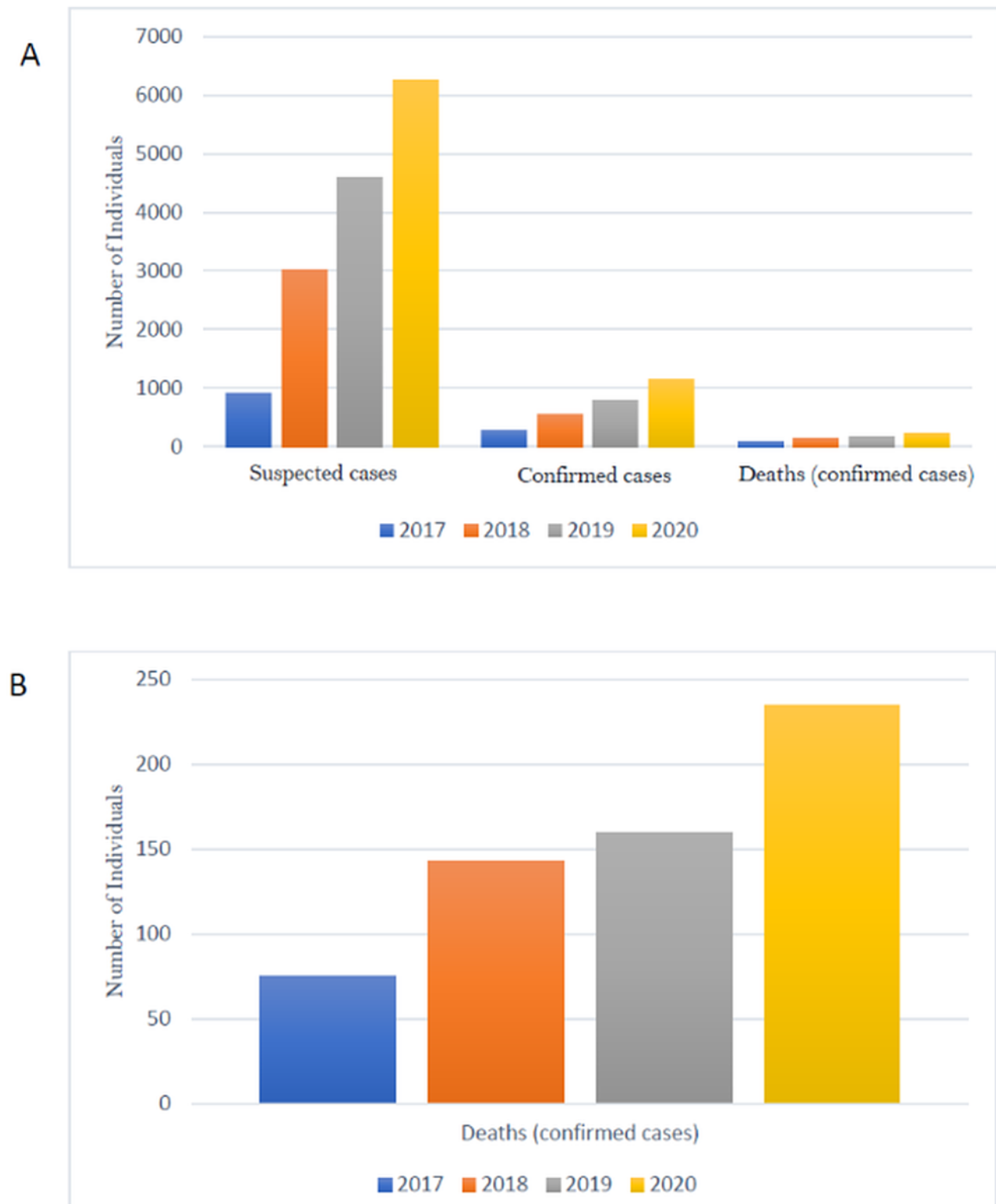
the epidemic curve of Lassa fever in Nigeria has increased from 2017 till date (Figure 1). Therefore, we hypothesize that Lassa virus strains fueling the epidemic since 2017 and onwards are distinct from those isolated before 2017 in terms of small-scale mutations but not overall phylogenetic clustering patterns. Therefore, our proposed study would focus on determining the mutational profile of Lassa virus strains isolated in 2018 and 2019 and to compare them with isolates from previous years, identify gene trees that may serve as surrogates for species trees, and help reconstruct the time-scaled evolution of Lassa virus in Nigeria.

To our knowledge, no studies have reported a marker gene for Lassa virus in Nigeria. The identification of a gene or combination of genes that serve as surrogates for species trees would facilitate real-time monitoring of Lassa virus evolution and transmission and aid in routine diagnosis of Lassa fever. A demonstration of phylogenetic congruence between gene trees and the S and L segment trees would provide evidence supporting the utility of such a gene as a marker for Lassa virus whole-genome phylogeny.

There is a paucity of information regarding genome-wide mutational analysis of Lassa virus isolated in Nigeria in 1969-2019. Comparative mapping of mutations (indels and single nucleotide polymorphisms [SNPs]) in the Lassa virus genomes may provide mutation signatures of Lassa virus. Although the potential mutational differences between strains isolated in 2018-2019 and before 2018 (1969-2017) would not provide insights into the increased transmissibility of the virus in Nigeria in and after 2018, functional analysis of the identified mutations in future studies would provide valuable insights into the role of indels and SNPs (if any) in Lassa virus infections. Hence, *in silico* mapping of mutations in the virus genomes before future functional analysis of identified mutations would be suitable.

Although Ehichioya et al [14] constructed time-scaled maximum clade credibility trees for Lassa virus isolated in Nigeria, they did not include strains from 2019; they analyzed only S and L segments but did not include genes encoding the Z protein, L polymerase, nucleoprotein, and glycoprotein. Furthermore, they did not perform congruence tests to determine whether the S segment tree is congruent with the L segment tree. Our proposed study will address the aforementioned knowledge gaps in an attempt to provide an updated evolutionary insight into Lassa virus in Nigeria.

Figure 1. (A) Year-by-year trends in the epidemiology of Lassa fever in Nigeria showing total suspected cases, confirmed cases, and the death toll for confirmed cases as reported by the Nigerian Center for Disease Control as at week 46 of every year. (B) Confirmed deaths due to Lassa fever in Nigeria for period 2017 to 2020.



Methods

Sequence Collection, Phylogenetic Analysis, and Congruence Test

Lassa virus sequences would be collected from GitHub [15] following sequencing efforts through a collaboration between the Irrua Specialist Teaching Hospital, Institute for Lassa Fever

Research and Control (Irrua, Edo State, Nigeria); the Bernhard-Nocht Institute for Tropical Medicine (Hamburg, Germany); the Rega Institute/KU Leuven (Leuven, Belgium); the ARTIC network; and Public Health England (PHE) (Salisbury, the United Kingdom). The collection includes sequences isolated from 1969 to 2019 and contains a total of 415 L segment sequences and 499 S segment sequences. The sequences, as seen in the GitHub repository [15], have their

noncoding segments excised. Owing to resource limitations, a subset of sequences for the L and S segments would be drawn from the original set. Members of the subset would be selected to represent all major and minor clades within the Lassa virus population. After collection, the sequences would be aligned using MAFFT (version 7.450) using the default settings [16]. After alignment, Bayesian phylogenetic analysis would be performed using BEAST (version 2.6.2) [17]. The analysis would be performed using the strict clock and the coalescent constant population tree prior parameters. Custom priors would be added to check for the time to the most recent common ancestor for the 2018 and 2019 virus isolates. The tree file generated as output from Bayesian analysis would be used to construct a time-scaled maximum clade credibility tree by using TreeAnnotator (version 2.6.2) [17], and this tree would be visualized using FigTree (version 1.4.4) [18] where a timescale would be added with the specimen collection date for calibration. The aforementioned steps from alignment to phylogenetic analysis would be repeated for each gene. Genes can be extracted from each genome segment through the annotation provided by National Center for Biotechnology Information [19,20]. Finally, congruence tests between the gene and segment phylogenies would be conducted using the Kishino-Hasegawa, Shimodaira-Hasegawa, and approximately unbiased tests using IQ-TREE 2 [21,22] with default parameters.

Sequence Similarity Matrix and Mutation Mapping

The percent identity matrix of both segments of the *Mammarenavirus* genome would be obtained using the

Base-By-Base bioinformatics program [23]. Owing to the large number of sequences, the percent identity matrix would only be obtained for a small fraction of the entire set of sequences, which is highly representative of the general population.

The 2018 and 2019 isolates would be extracted from these gene sequence alignments. All gaps would be deleted to produce the raw order of bases in all isolates. Thereafter, all sequences would be translated in silico into amino acid sequences, and the reference sequence for each protein [24-27] would be added. After amino acid sequence alignment, the web-based tool DIVEIN [28] would be used to call out variable sites within all protein sequences, which can then be visualized in Microsoft Excel.

Results

This study commenced in January 2020 as an obligatory senior undergraduate research project of the first author (DK) and will be completed in February 2021 with a thesis presentation and defense. Data mining and alignment of Lassa virus genome sequences have been completed. Phylogenetic and genomic analysis of aligned Lassa virus genome sequences are currently ongoing. A total of 133 L and 145 S segments from 1969 to 2019 were used for the genome-wide mutational and phylogenetic analyses (Table 1). Segment lengths upon multiple sequence alignment with gaps removed for the L and S segments and 4 genes are depicted in Table 2.

Table 1. Number of sequences of the L and S segments of the Lassa virus genome from 1969 to 2019 used in this study.

Year	Number of Lassa virus genome sequences	
	L segment	S segment
1969	1	1
1974	0	1
1976	1	1
1977	0	1
1981	1	2
1982	1	1
1999	1	1
2000	2	2
2003	1	1
2008	11	11
2009	12	12
2010	10	11
2011	12	10
2012	14	13
2013	4	8
2014	3	4
2015	3	5
2016	12	13
2017	3	3
2018	21	24
2019	20	20
Total	133	145

Table 2. Sequence length (nt) of aligned segment and gene sequences after gap removal.

Segment	Length of the aligned sequence (nt)
L segment	6809
Z protein	297
L polymerase	6512
S segment	3186
Nucleoprotein	1710
Glycoprotein	1476

Discussion

Unlike previous reports, this proposed study will focus on determining SNPs and indel profiles of the 2018 and 2019 isolates of Lassa virus using the reference sequences as a benchmark for comparison. The identification of such SNPs and indels may further our understanding of the molecular factors contributing to the upsurge in Lassa fever cases in Nigeria in 2018 till date. SNP and indel identification may also help explain the limited instances of potential human-to-human transmission of Lassa fever as suggested in a previous report [10]. The identification of a marker gene that predicts

whole-genome phylogeny can be useful in situations of limited resources. This marker gene can be sequenced and used for more rapid evolutionary analysis of Lassa virus. The inclusion of sequences from 2019 and congruence tests for tree topology in the reconstruction of a time-scaled maximum clade credibility tree will provide an updated and more robust analysis of Lassa virus evolution in Nigeria.

A major limitation of this proposed study is that the genome sequences of viruses isolated from rodent reservoirs during the 2018 outbreak are unavailable; hence, this study will not be able to examine whether the upsurge resulted from increased rodent-to-human transmission. A comparison of the genome

sequences of Lassa virus isolated from rodent reservoirs with those of the 2018 and 2019 human isolates would reveal sequence signatures that may be associated with increased rodent-to-human transmission. Thus, viral adaptation for increased transmissibility may have occurred in the rodent reservoir rather than in humans. Extensive retrospective and prospective sampling of the Lassa virus in reservoir hosts is needed to examine our hypothesis of rodent-to-human

transmission. Another limitation is that Lassa virus genome sequences from 2020 are not readily available.

The strengths of this proposed study include the public availability of Lassa virus genomes isolated during the 2018 and 2019 outbreaks, application of congruence tests to inferred phylogenetic trees, and mapping of mutations that may be masked by phylogenetic signals. Collectively, the strengths of this proposed study will more comprehensively elucidate the evolutionary history of Lassa virus in Nigeria.

Conflicts of Interest

None declared.

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Abbreviations

SNP: single nucleotide polymorphism

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Protocol

Telehealth Diabetes Prevention Intervention for the Next Generation of African American Youth: Protocol for a Pilot Trial

Abigail Gamble^{1,2,3*}, MS, PhD; Bettina M Beech^{4*}, MPH, DrPH; Breanna C Wade^{1*}, BS, MS; Victor D Sutton^{1,5*}, MPPA, PhD; Crystal Lim^{6*}, PhD, ABPP; Shanda Sandridge^{7*}, MSN, CPNP-AC; Michael A Welsch^{8*}, MS, PhD

¹Department of Preventive Medicine, John D Bower School of Population Health, University of Mississippi Medical Center, Jackson, MS, United States

²Department of Pediatrics, School of Medicine, University of Mississippi Medical Center, Jackson, MS, United States

³Myrlie Evers-Williams Institute for the Elimination of Health Disparities, John D Bower School of Population Health, University of Mississippi Medical Center, Jackson, MS, United States

⁴Department of Health Systems and Population Health Science, College of Medicine, University of Houston, Houston, TX, United States

⁵Office of Preventive Health and Health Equity, Mississippi State Department of Health, Ridgeland, MS, United States

⁶Division of Psychology, Department of Psychiatry and Human Behavior, University of Mississippi Medical Center, Jackson, MS, United States

⁷Pediatric Gastroenterology, Children's Healthcare of Mississippi, Jackson, MS, United States

⁸Department of Population Health Science, John D Bower School of Population Health, University of Mississippi Medical Center, Jackson, MS, United States

* all authors contributed equally

Corresponding Author:

Abigail Gamble, MS, PhD

Department of Preventive Medicine

John D Bower School of Population Health

University of Mississippi Medical Center

2500 N State St

Jackson, MS, 39216

United States

Phone: 1 6018159065

Email: agamble2@umc.edu

Abstract

Background: In 1999, type 2 diabetes mellitus (T2DM) was identified as an emerging epidemic in youth, and racial and ethnic minority youth were identified with high risk. Two decades later, no gold standard T2DM prevention intervention has been established for this population.

Objective: This study tests the efficacy of a telehealth diabetes prevention intervention for African American (AA) families with children with risk for T2DM. Concurrently, investigators aim to evaluate an implementation strategy for the uptake of the intervention by the University of Mississippi Medical Center's (UMMC) pediatric weight management clinic.

Methods: This single-arm trial will enroll 20 parents with overweight or obesity of children (8-11 years) with overweight or obesity, both of whom are at risk for T2DM. Parents will meet in small groups (5 parents per group) weekly for 11 weeks and then monthly for 4 monthly maintenance sessions via videoconference using Wi-Fi-enabled iPads with cellular connectivity. The intervention will be adapted from the National Diabetes Prevention Program and *Power to Prevent*, a diabetes prevention program tailored for AA families. The same lifestyle intervention facilitated by a racially concordant lifestyle coach trained in the Diabetes Prevention Program will be delivered to all groups (n=4). Participants will be recruited in-person during patient encounters at the UMMC's pediatric weight management clinic. Sessions will consist of dietary and physical activity behavior change strategies facilitated using problem-solving and goal-setting skills. The implementation strategy has 2 targets: the pediatric weight management clinic site and clinical team and parents of children at risk for T2DM engaged in intensive obesity treatment to prevent T2DM. The multifaceted implementation protocol includes 4 discrete strategies: creating a new clinical team, changing the service site, intervening with families, and promoting organizational readiness for change.

Results: Recruitment and enrollment began in December 2020, and the intervention is scheduled to be delivered to the first cohort of parents in March 2021. The results are expected to be submitted for publication beginning in November 2021 through 2022. The primary outcome measure for the pilot trial will include changes from baseline to 12 and 30 weeks in the child BMI

z score and parent BMI. The implementation evaluation will include multiple measures of feasibility, acceptability, appropriateness, fidelity, and efficacy. This protocol was approved by the UMMC's Institutional Review Board (#2020V0249).

Conclusions: The proposed intervention approach is supported by the scientific literature and is scalable given the current and future health care subsidies for telehealth. Findings from this pilot trial will begin to address critical barriers to defining a gold standard lifestyle intervention for AA families with children at risk for T2DM. If effective, the intervention could be feasibly disseminated to treat obesity and prevent T2DM in high-risk AA pediatric populations.

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KEYWORDS

prediabetic state; child obesity; telehealth; obesity management; behavioral science; implementation science; Jackson Heart Study; Centers for Disease Control and Prevention; preventive medicine; mobile phone

Introduction

Background

In 1999, Rosenbloom and Winter [1] labeled type 2 diabetes mellitus (T2DM) in youth as an emerging epidemic, identifying racial and ethnic minority groups, whose proportion in the US population continues to increase [2], at highest risk. T2DM is a chronic state of hyperglycemia that clusters in families because of genetic, cultural, behavioral, and environmental risk factors [3,4]. In 2018, an estimated 32.4 million (10.5%) people of all ages in the United States had T2DM, and an additional 88 million adults (34.5%; ≥ 18 years) and 1 in 5 youths (12-18 years) were estimated to have had prediabetes [5,6]. Predictions indicate that with rising incidence rates, the proportion of US youth (<20 years) with T2DM may quadruple between 2010 (22,820 youths) and 2050 (84,131 youths [7]), and African American (AA) youth represent a vulnerable pediatric population with high risk [7,8].

Alarming, T2DM presents a more severe and aggressive disease course in youth than in adults [9], and there is no optimal treatment for T2DM in youth [10]. In a retrospective analysis of youth and adults with obesity and impaired glucose tolerance, adolescents experienced more severe insulin resistance than adults with similar adiposity and glycemic status [9]. Of particular concern are the results from the recent RISE (Restoring Insulin Secretion) Pediatric Medication Study that evaluated whether β -cell function and metabolic control could be effectively altered by a pharmacological intervention [11]. Results from this randomized controlled trial with 91 pubertal youths (10-19 years) with obesity and existing impaired glucose tolerance randomized to 12 months of metformin showed that the early pharmacologic intervention was ineffective in slowing disease progression [11]. These findings underscore the need for strategies to prevent or delay the onset of T2DM in youth at high risk [12].

Prediabetes is a precursor to T2DM, characterized by hyperglycemic parameters below the diabetes threshold [13,14]. An estimated 5% to 10% of prediabetes cases advance to T2DM per annum [15], and according to the American Diabetes Association (ADA), up to 70% of people with prediabetes will progress to T2DM at some point in their lifetime [16]. Although prediabetes may never progress to T2DM, unfavorable cardiometabolic profiles remain among people with prediabetes,

putting them at increased risk for cardiovascular-related morbidities and premature mortality [17]. Consequently, youth with prediabetes are faced with earlier and prolonged exposure to myriad cardiometabolic abnormalities, accentuating the critical need for obesity treatment in the primary prevention of T2DM in youth [7,10].

Diabetes Prevention

Studies have indicated that adults with prediabetes can mitigate T2DM prognosis by taking preventive action, such as participation in the National Diabetes Prevention Program (DPP) [18]. The DPP began as a multisite randomized controlled trial, which demonstrated the effectiveness of a 12-month intensive lifestyle intervention over pharmaceutical treatment for preventing or delaying T2DM among adult participants with prediabetes across all racial and ethnic groups [19]. At 2.8- and 10-year follow-up, participants randomized to the lifestyle intervention group reduced their risk of developing T2DM by 58% and 34% compared with 31% and 18% in the metformin group, respectively [20,21]. In 2010, US Congress authorized the Centers for Disease Control and Prevention to lead the dissemination of the DPP [18] as a targeted strategy and population approach to reduce the incidence of T2DM among adults with prediabetes [22].

Intensive lifestyle modification is the recommended treatment for pediatric patients with prediabetes [23]; however, there is no gold standard lifestyle intervention to prevent T2DM in youth. Previous studies have demonstrated the feasibility of lifestyle interventions for youth with overweight or obesity and those at risk for T2DM and the importance of tailored interventions for racial and ethnic minority groups; however, limited efficacy has been shown in reducing T2DM risk and improving obesity outcomes [24-26]. Intervention studies with youth have also been hindered by the insufficient representation of racial and ethnic minority youth at high risk for T2DM in obesity treatment trials [27]. *Power to Prevent* is a diabetes prevention intervention from the Centers for Disease Control and Prevention based on the DPP and tailored for AA families [28]. To our knowledge, this intervention has not yet been evaluated among AA families with children at risk for T2DM or disseminated through health care institutions. Given the restrictions on in-person gatherings because of the COVID-19 pandemic and the consistent literature reporting high attrition rates among in-person interventions, there is a need for novel

and sustainable implementation modalities for delivering lifestyle interventions to racial and ethnic minority families at high risk for T2DM [24].

Telehealth has demonstrated effectiveness in delivering obesity and prediabetes treatment [29-33] and has mitigated barriers to accessing care for millions of Americans [31]. In particular, videoconferencing has been widely used to deliver effective T2DM care for adult and young patients [33-36] and has recently established efficacy for group-based interventions [37-39]. In a review of 17 lifestyle intervention studies, the authors found that tablet-based group videoconferencing was feasible, accessible, and acceptable, regardless of participants' digital literacy (technology skills) [37]. Across studies, videoconferencing groups cultivated cohesiveness and bonding similar to in-person settings, and participants developed behavioral skills including lifestyle behaviors to treat obesity and demonstrated improved health outcomes along with high attendance rates (66%-93.8%) and few dropouts [37]. Intervention group sizes averaged from 5 to 7 participants and met weekly for 1 hour over 12 to 26 sessions in total [37]. The use of telehealth technology to deliver a family-based lifestyle diabetes prevention intervention tailored for AA families is likely to offer a scalable approach to reduce T2DM among high-risk youth [40-42].

Objectives

The Telehealth Diabetes Prevention Intervention for the Next Generation of African American Youth (TELE-GEN) pilot trial proposes implementing and evaluating a diabetes prevention intervention based on the *Power to Prevent* program for AA parents of children (8-11 years) who are both overweight or obese and at risk for T2DM. Historically, a lengthy effectiveness study conducted under *ideal circumstances* would be the next step in identifying a gold standard lifestyle intervention to prevent T2DM in AA youth; however, standard effectiveness studies are limited by their inability for rapid translation and the need for subsequent implementation studies to validate utility in real-world settings [43]. Hybrid research designs leverage the rigor of clinical trials and implementation science to foster rapid translation and effective implementation [33,43]. Thus, in partnership with the Center for Telehealth at the University of Mississippi Medical Center (UMMC) and pediatric weight management clinic, we propose a novel effectiveness-implementation hybrid type II research design [43] with the coprimary aim to (1) conduct a 30-week, single-arm pilot trial with at-risk parents of at-risk children to assess the early efficacy of Power to Prevent delivered using small group-based videoconferencing to reduce BMI in parents ($n=20$) and stabilize or reduce BMI z scores in children ($n=20$), while (2) conducting a comprehensive evaluation of a multifaceted implementation strategy for the uptake of the intervention by the pediatric weight management clinic at the UMMC in Jackson, Mississippi. The protocol described below was approved by the UMMC's Institutional Review Board (#2020V0249).

Methods

Study Setting

The Diabetes Belt is a distinct geographic region in the southern United States where county-level adult T2DM rates ($\geq 11\%$) are especially high and obesity and physical inactivity account for one-third of all diagnosed cases [44]. Mississippi is the only state in which every county (82 counties) is represented by the Diabetes Belt. According to America's Health Rankings 2019 Report, Mississippi had the third-highest adult T2DM rate (14.3%) in the United States, followed by the second highest adult obesity (39.5%) and physical inactivity (32%) rates [45]. Recent data from the National Survey of Children's Health (2018-2019) reported in the State of Obesity Report, 2020 [46], identified Mississippi as having the second-highest youth (10-17 years) obesity rate (22.3%) nationally. In addition, AA adults (45.7% [45]) and youth (25.4% [47]) had higher rates of obesity compared with their White counterparts (36.3% [45] and 21.7% [47], respectively). Mississippi also has the highest percentage of Black population (37.8% [48]), and 42% of Mississippi youth are Black compared with 14% nationally [49]. Mississippians experience persistently high rates of poverty (19.7%) and child poverty (27%) [48], and the state is mostly rural and medically underserved [50]; social and environmental factors contribute to poor health and disease. In this context, AA youth in Mississippi are among those at highest risk for T2DM.

The UMMC is the state's only academic medical center and has the only children's hospital in the state. In 2019, 4464 AA children aged 8 to 11 years were treated by a UMMC pediatric clinic, and between November 2019 and April 2020, 170 AA children aged 8 to 11 years were identified with the risk for T2DM in the UMMC's Prediabetes Registry. UMMC is a minority-serving, research-intensive health care organization with a state-mandated requirement to provide not less than 50% of their services to indigent persons (Mississippi Legal Code Annotated 37-115-27; 2017). The UMMC is also a national leader in telehealth [51] and has one of only 2 National Centers of Excellence in Telehealth in the nation [52]. The UMMC Center for Telehealth has successfully intervened with adults with uncontrolled T2DM [53] using remote patient monitoring and is piloting a similar single-arm feasibility trial with pediatric patients (10-17 years) [54]. Health systems with telehealth technology are encouraged to implement and evaluate weight loss interventions for patients at risk for T2DM [32,40,55], and Mississippi is at the forefront of advancing telehealth and adopting mandates for telehealth care reimbursement [51-53,56]. Thus, Mississippi is an ideal location to test the effectiveness and implementation of lifestyle interventions using telehealth in clinical care settings to treat obesity and prevent T2DM in AA youth at the highest risk for diabetes in the United States.

Participant Recruitment and Sample Size

In-person participant screening and enrollment will be conducted in the UMMC pediatric weight management clinic beginning in December 2020. Preliminary screening will be conducted by the clinical provider using a patient eligibility checklist that will screen for both child and parent eligibility. The lifestyle coach will immediately meet in the clinic room following the

clinical encounter to conduct a full screening and provide detailed study information to interested parents and children. Consent forms will be verbally described to parents and children, and parent consent, parent permission, and child assent will be obtained before study enrollment.

Children will be eligible to participate if they are AA, overweight or obese (≥ 85 th percentile for age- and sex-specific BMI), and aged between 8 and 11 years. The child age range was selected to allow for intervention occurring before the average age of youth-onset T2DM, 13 years [10]. The criteria for parents (biological, grandparent, or legal guardian) of eligible children included AA, overweight or obese ($\text{BMI} \geq 25 \text{ kg/m}^2$), and coresidence with the child. Although mothers represent most participants in family-based studies, we will not use parents' sex as an inclusion criterion. Parents and children must also be at risk for T2DM based on the following criteria: (1) parents' T2DM risk will be assessed using the A1CNow⁺ system to measure point-of-care hemoglobin A_{1c} (HbA_{1c}), which uses a drop of nonfasting blood (5.7%-6.4%), and the ADA prediabetes screening tool (score ≥ 5); (2) child risk will be based on the BMI percentile (≥ 85 th percentile) and parents' risk (BMI ≥ 25 and ADA screening or HbA_{1c}).

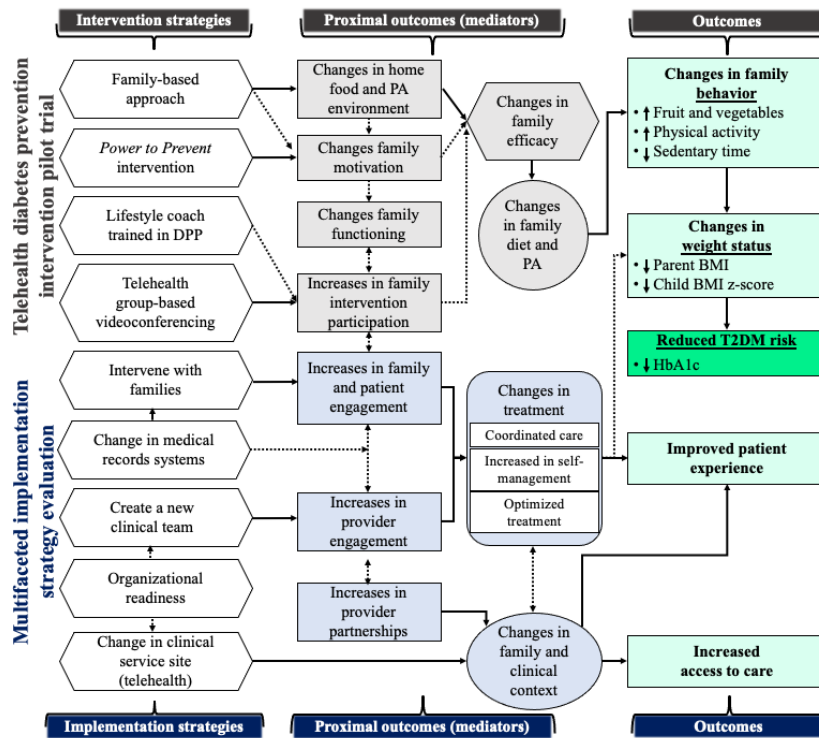
Consistent with previous T2DM prevention interventions [26,57], we will exclude families if the child or parent has a history of T2DM or a screening HbA_{1c} level greater than 6.4%, is taking glucose-lowering medications, is participating in a supervised weight loss program, is pregnant or breastfeeding, has conditions limiting participation, has undergone weight loss surgery, or is moving out of state within 6 months. If a parent becomes pregnant during the study, we will include only child data (index participant) in the analyses. Technology literacy will not be included as an exclusion criterion. Participants will receive technology instruction from the telehealth center and be provided technical support as needed.

The power calculation, across 5 scenarios, shows detectable effect sizes, ≥ -2.5 (SD 0.05) BMI in parents [58] and in children, where a modest reduction in BMI z score (≥ 0 to < -0.1 , SD 0.05) has been associated with improved cardiometabolic risk [59]. In the first 3 scenarios, assuming 10% attrition [37], a minimum of 18 dyads are needed. In scenarios 4 and 5, detectable effect sizes are reported in the case of 0% ($n=20$ dyads) and 20% ($n=16$ dyads) attrition. We anticipate 20% attrition, which is consistent with the group- and family-based telehealth lifestyle intervention literature [60-62]. Analyses are based on $\alpha=.05$ and a conservative two-sided test. An effect size of 1.0 is considered substantial and 0.5 is considered medium. We will obtain reliable effect size estimates to design a pilot randomized controlled trial.

Conceptual Model

Family Systems Theory, undergirded by family motivation and Social Learning Theory, and the Telehealth in Chronic Disease (TECH) model are the foundations for the TELE-GEN conceptual model (Figure 1). Social Learning Theory is used to guide intensive lifestyle interventions, such as the DPP [63]. The conceptual basis for the TELE-GEN intervention has evolved from pediatric obesity and T2DM prevention research using Family Systems Theory [64,65] and Social Learning Theory [66,67]. Successful Social Learning Theory-based intervention approaches include helping families make changes to the home food, physical activity, and screen time environment, increasing family motivation to make positive changes, and increasing family functioning around food, physical activity, and sedentary behaviors. These activities are thought to increase family efficacy for making lifestyle modifications and ultimately improving intervention outcomes. This theoretical approach is bolstered by applying the TECH model, which outlines effective pathways for the uptake of clinical telehealth interventions [68]. The TELE-GEN conceptual model is displayed in Figure 1.

Figure 1. Telehealth diabetes prevention intervention and implementation conceptual model. DPP: Diabetes Prevention Program; PA: physical activity.



Intervention

Power to Prevent [28] is a diabetes prevention intervention based on the DPP [63] and the *Small Steps, Big Rewards Program* [69] and is tailored for AA families. The goal of the program is to achieve a 5% to 7% weight loss by making modifications to dietary, physical activity, and sedentary behaviors. In the proposed pilot trial, modification to family dietary, physical activity (≥ 150 min per week), and sedentary behaviors will be targeted, in addition to individual-level parent behaviors. The *Power to Prevent Leader Guide* and participant materials will be adapted and used in each session. The scientific literature strongly supports family-based approaches to treating youth with overweight or obesity [70]. Thus, group-based sessions (60 min) will be conducted with parents and target the adoption, maintenance, and self-regulation of family-focused dietary, physical activity, and sedentary behaviors. Parent participants will meet weekly for 11 weeks and then monthly for 4 pilot maintenance sessions (15 sessions in total; frequency and duration supported by the literature [71]). Sessions for all groups will be facilitated by a racially concordant lifestyle coach (interventionist) who will be trained in accordance with the Centers for Disease Control and Prevention Diabetes Prevention Recognition Program standards [72]. Wi-Fi-equipped iPads (12.9”) with cellular connectivity will be used to link families to videoconferencing sessions and to cooking and family-friendly physical activity video demonstrations via YouTube.

Intervention Targets

In 2013, an obesity expert panel reviewed 146 lifestyle intervention studies and reported a high degree of evidence for the effectiveness of diet with caloric restriction and increased physical activity for weight loss in adults [73]. Behavioral

interventions to treat obesity are deemed safe for youth (4-18 years); however, fostering healthy eating behaviors is recommended over caloric restriction for weight loss in youth [74]. Thus, the dietary targets for children are to increase fruit and vegetable consumption, reduce sugar-sweetened beverage intake, and adopt appropriate portion sizes. The dietary targets for parents are to reduce the overall caloric intake by reducing the consumption of sugar-sweetened beverages and dietary fat and to increase fruit and vegetable intake. According to the 2018 Physical Activity Guidelines [75] and the 2009 American College of Sports Medicine Position Statement [76], the family (parent and child) physical activity goal is 60 minutes of moderate-to-vigorous activity (3 or more metabolic equivalents) per day on 5 or more days per week. In addition, based on the recommendations for treating obesity and reducing T2DM risk in youth, the sedentary target will be to reduce out-of-school time watching television, playing video games, and/or using a tablet, iPad, or smartphone to less than 2 hours per day.

Intervention Sessions

Group sessions will consist of identifying behavior change strategies leading to achieving the intervention targets (20 minutes), problem solving and decision making to circumvent barriers (20 minutes), and family goal setting and action planning (20 minutes). Parents will be coached to self-select behavior change strategies and practice skills that will enable them to do things such as making healthy foods available in the home, modifying recipes to be healthier, reading food labels, increasing family physical activity, and creating boundaries for the use of technology to reduce out-of-school sedentary time. Parents will be encouraged to use behavioral reinforcement strategies with their children, such as giving immediate praise, creating realistic expectations, and rewarding effort [77]. The

practice of brainstorming will be used to encourage parents as a collective group to self-discover solutions to behavior change barriers and support participants in achieving their goals. Brainstorming has proven to be an effective component of problem solving and mitigating barriers to sustainable behavior change [78-82]. Action planning will be used to facilitate parents in setting realistic, attainable, and short-term (weekly) goals for making dietary and physical activity changes. Goal setting positively correlates with weight loss [83], and action planning is an effective self-monitoring strategy that will allow participants to personalize their goals and gradually achieve intervention targets [84,85].

Intervention Participant Retention

Telehealth is an effective retention strategy used in the DPP [86] and mitigates transportation barriers [87]. The lifestyle coach will dedicate time outside of intervention sessions to build rapport with parents and will function as a personal contact for participants to establish meaningful relationships, send meeting reminders, and schedule and conduct make-up sessions (consistent with DPP [63]) [86]. Participants will be incentivized using attendance raffles for cooking (eg, measuring cups), physical activity equipment (eg, jump rope), and incremental monetary compensation at each assessment point (baseline, US \$50; postintervention, US \$75; follow-up, US \$150) [86]. Study assessments will be conducted in-person at the time of the child's routine appointment with the pediatric weight management clinic and monetary resources will be allocated to families experiencing transportation barriers.

Intervention Efficacy Measures

Primary and secondary outcome measures will be assessed at baseline (week 1), postintervention (week 12), and 4-month follow-up (week 30). The primary outcome measure will be a reduction or stabilization in the child BMI z score (index participant) and a reduction in parent BMI (coparticipant) [88]. Secondary outcomes include anthropometric (waist circumference and body composition), biomarker (HbA_{1c}, blood pressure, resting heart rate, lipid profile, and Tanner stage), behavioral (fruit and vegetable, sugar-sweetened beverage, and sweat and salty snack consumption; family meal frequency; fast food meal frequency; physical activity volume; and sedentary time), psychosocial (self-efficacy, self-regulation, readiness to change, family functioning, and perceived stress), and environmental (home food and physical activity environment and perceived neighborhood support for healthy eating and physical activity) measures (Table 1). All the measurements will be recorded electronically using REDCap (Research Electronic Data Capture) tools hosted at the UMMC [89]. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing an intuitive interface for validated data capture; audit trails for tracking data manipulation and export procedures; automated export procedures for seamless data downloads to common statistical packages; and procedures for data integration and interoperability with external sources.

Table 1. Pilot trial outcome measures.

Outcome measure and instrument	Participant
Anthropometric measures	
BMI z score	
Stature (0.1 cm) assessed using Seca stadiometer, and weight (0.1 kg) assessed using Tanita (TBF-400) body composition and weight scale; height and weight measured without shoes; BMI z score using a CDC ^a SAS program for the 2000 growth charts ages 0 to <20 years [90]	Child
BMI	
Stature (0.1 cm) assessed using Seca stadiometer, and weight (0.1 kg) assessed using Tanita (TBF-400) body composition and weight scale; height and weight measured without shoes; BMI calculated using the CDC formula: weight (kg)/(height [m]) ² [91]	Parent
Body composition	
Tanita (TBF-400 Body Composition Monitor) uses bioelectrical impedance to assess fat and fat-free mass	Parent and child
Waist circumference	
Seca 203 ergonomic circumference measuring tape	Parent and child
Biomarker measures	
HbA_{1c}^b	
A1CNow ⁺ system [92]; patient-friendly, point-of-care fingerstick with 5 µl blood (nonfasting)	Parent and child
Lipid profile	
CardioChek Plus Analyzer [93]; patient-friendly, point-of-care fingerstick with 15-40 µl blood; measures total cholesterol, high-density lipoprotein, and triglycerides	Parent and child
Systolic blood pressure	
IntelliSense professional digital blood pressure monitor using the American Heart Association guidelines for children and adults [94]	Parent and child
Diastolic blood pressure	
IntelliSense professional digital blood pressure monitor using the American Heart Association guidelines for children and adults [94]	Parent and child
Resting heart rate	
IntelliSense professional digital blood pressure monitor using the American Heart Association guidelines for children and adults [94]	Parent and child
Psychosocial measures	
Self-efficacy	
Parental self-efficacy, 14 items (Norman et al [95]); subscales: confidence for encouraging healthy behaviors and role modeling healthy behaviors	Parent
Healthy Eating and Physical Activity Self-Efficacy Questionnaire, 10-items (Lassetter et al [96]); modified to assess a sedentary environment (2 items)	Child
Home physical and social environment	
Modified Home PA and Food Environment Scale, 100 items (Gattshall et al [97]); subscales: availability and accessibility of food, physical activity equipment, and technology devices; parent role modeling and family policies for food, physical activity, and technology use	Parent
Motivational readiness to change	
Family Motivational Readiness, 8 items (Rhee et al [98,99]); modified to assess technology and all questions with regard to child and family, 16 items total; subscales: helping child and family eat healthy, physical activity, and limit technology	Parent
Family functioning	
McMaster Family Assessment Device, 60 items (Epstein et al [100]; Halliday et al [101]); subscales: problem solving, communication, roles, affective responsiveness, affective involvement, behavior control, and general functioning	Parent
Neighborhood perceptions	

Outcome measure and instrument	Participant
Neighborhood Perceptions Scale, 31 items (Mujahid et al [102]); subscales: aesthetic quality, walking environment, food availability, safety, violence, social cohesion, and activities with neighbors	Parent
Stress	
Perceived Stress Scale, 10 items (Cohen et al [103])	Parent
PROMIS Pediatric Psychological and Physical Stress Scale, 19 items and 26 items (Bevans et al [104])	Child
Behavioral measures	
Child behavior (subjective)	
Child Obesity Behavior Questionnaire; 20 items to measure parents' perception of the child's dietary, physical activity, and sedentary behaviors (Rhee et al [98])	Parent
Healthy Eating and Physical Activity Recall Questionnaire, 9 items (Lassetter et al [96]), modified to assess technology environment, and 5 items	Child
Physical activity volume (objective)	
ActiGraph GT9X Accelerometer; device worn on the wrist of the nondominant hand for 7 consecutive days to measure volume of moderate-to-vigorous physical activity minutes (greater than 3 metabolic equivalents)	Parent and child
Sedentary time (objective)	
ActiGraph GT9X Accelerometer; device worn on the wrist of the nondominant hand for 7 consecutive days to measure volume of low-intensity activity minutes (less than 3 metabolic equivalents)	Parent and child
Other measures	
Pubertal stage	
Pubertal Development Scale, 5 items (Carskadon and Acebo [105])	Parent and child

^aCDC: Centers for Disease Control and Prevention.

^bHbA_{1c}: hemoglobin A_{1c}.

Data Analysis

Participant sociodemographic characteristics at baseline will be described using means and SDs, medians and ranges, or frequencies with percentages where applicable. The primary outcome evaluation will assess the change in child BMI *z* score (index participant) and parent BMI (coparticipant) from baseline to 12 and 30 weeks using repeated measures analysis of covariance with child Tanner stage as the covariate. Secondary analyses will include the comparison of anthropometric, biomarker, behavioral, psychosocial, and environmental measures adjusted for other factors. Generalized linear modeling will be used to assess the effect of the intervention, both unadjusted and adjusted (controlling for demographics, baseline BMI *z* score, and BMI). Data will be analyzed according to intention-to-treat principles [106-108].

Implementation Strategy

The proposed implementation strategy has 2 targets: (1) the UMMC's pediatric weight management clinical setting and clinical care team, which will be modified to support the uptake of the intervention and integration of the lifestyle coach into the clinical care team and (2) parents and children with T2DM risk referred to and engaged in intensive obesity treatment for the prevention of T2DM. The multifaceted implementation plan includes 4 discrete strategies: (1) creating a new clinical team, (2) changing the service site, (3) intervening with families, and (4) assessing organizational readiness [109]. In accordance with the recommendations for reporting implementation protocols [110], each strategy is operationalized in Table 2.

Table 2. Operationalization of discrete implementation strategies.

Strategy components	Discrete strategy			
	Create a new clinical team	Change service sites	Intervene with families	Readiness for change
Actor	Nurse practitioner; psychologist; lifestyle coach	Lifestyle coach; parent groups	Lifestyle coach; parent groups	Nurse practitioner; psychologist; lifestyle coach
Action	Nurse practitioner referral to lifestyle coach for screening and enrollment	Intervention delivered via videoconference; lifestyle support mirroring clinical treatment	Lifestyle coach provides support and conducts weekly outreach with parents	Identify barriers and facilitators, and processes impacting intervention uptake
Target	Integrate lifestyle coach as part of the clinical care team	Mitigate barriers to participation and engage the parent in treatment	Mitigate barriers, retention, and engagement	Health system and clinic workflow context
Dose	Continuous	Weekly (×11) and monthly (×4)	Point of referral to follow-up	Continuous
Outcome	Acceptability; feasibility; appropriateness	Acceptability; feasibility; appropriateness; fidelity; efficacy	Acceptability; feasibility; appropriateness; fidelity; efficacy	Acceptability; feasibility; appropriateness
Justification	American College of Physicians supports clinical care teams [111]; team-based lifestyle care for diabetic patients has been effective [112]	TECH ^a model [68]; telehealth is practical given the COVID-19 pandemic [113]; an effective retention strategy [86] and mitigates transportation barriers [87]; videoconference is feasible, accessible, and acceptable [37]	Family Systems Theory [64,65]; Social Learning Theory [66,67]; TECH model [68]	Consolidated Framework for Implementation Research [114,115]

^aTECH: Telehealth in Chronic Disease.

Implementation Evaluation

An iterative formative and process evaluation will be conducted to explore the complex processes, dynamic context, and organizational influences on implementation [116]. A mixed methods realist approach will be used to determine the extent to which the intervention was delivered as intended and whether the implementation strategy was acceptable, appropriate, and feasible [117]. Similar complex designs have been used to evaluate the implementation of lifestyle interventions with new populations and within new settings [116,118-121].

Evaluation Participants

The pediatric nurse practitioner, clinical psychologist, lifestyle coach (herein referred to as *providers*), and parent participants (herein referred to as *families*) will be asked to participate in our evaluation. The principal investigator (PI) will concurrently, independently, and iteratively collect quantitative and qualitative data throughout the trial. Data collection instruments will be developed in REDCap [89] and iPad accessible. Intervention sessions and study team meetings will be conducted and recorded using Big Blue Button, an open source web conferencing system. Attendance and outreach records will be recorded in a password-protected Microsoft Excel file.

Evaluation Data Sources

Five data sources will be used to gather sufficient evaluation data. Brief qualitative interviews will be conducted with providers (across and within waves) and families (within waves) at 3 time points: (1) during the intervention, (2) at postintervention, and (3) at follow-up. Family interviews during the intervention will be conducted by the PI via phone at the families' convenience, and postsession and follow-up interviews will be conducted in-person during study assessments at the

clinic. Provider interviews will be conducted by the PI via Big Blue Button on the UMMC campus. Interviews will probe providers' and families' perceptions of the acceptability, feasibility, and appropriateness of the intervention and the impact of telehealth on patient and provider engagement, provider partnerships, treatment outcomes, and access to care. Providers and the PI will also meet weekly for 30 minutes via Big Blue Button to review protocols, discuss implementation progress, identify barriers and solutions, and create action plans for adaptations to improve recruitment, retention, and intervention delivery.

Parents and the lifestyle coach will be asked to complete brief postsession surveys using their iPads to assess the acceptability and appropriateness of the intervention content, materials, and delivery. The lifestyle coach will be asked to document participation, the *Power to Prevent* resources that were used, and session components that were delivered and be asked to describe what worked well and the obstacles encountered. The lifestyle coach will record formal attendance and outreach encounters to document participant attendance at each core session and maintenance session, make-up sessions, and any outreach encounters via email, phone, or text message. Session observations will be conducted by the PI using an observation guide during one-third of all sessions to assess implementation fidelity, family engagement, and interactions among families and the lifestyle coach (context).

Evaluation Measures

Five fidelity dimensions will be evaluated, including adherence, exposure, quality of delivery, participant responsiveness, and intervention differentiation [122]. Data sources will include brief postsession surveys, session observations, and attendance and outreach records. Four feasibility dimensions will be

evaluated, including recruitment, retention, engagement, clinical operations, and scheduling. Data sources will include interviews, surveys, session observations, attendance and outreach records, and meeting notes. Five acceptability dimensions will be evaluated, including changes in the clinical context and clinical team, changes in treatment, intervention materials, frequency and intensity of the intervention, and delivery via telehealth. Interviews and surveys will garner families' perceptions of the intervention, how their views evolved during the intervention, and opinions of the maintenance phase. Providers' and families' perceptions of the importance and benefit of the intervention, impact on access to and engagement in the intervention, optimization of obesity treatment, patients' experiences, and family and provider engagement will be assessed via interviews, surveys, and outreach and encounter records.

Data Analysis

Qualitative meeting notes and clinical and intervention observations will be reviewed and synthesized on an ongoing basis to make immediate adaptations to screening and enrollment procedures, implementation strategies, and intervention session delivery and facilitation. All other evaluation data analyses will be conducted in 3 phases. In phase 1, qualitative and quantitative data sources will be independently analyzed. In phase 2, we will use a side-by-side comparison convergence approach where the qualitative findings are outlined and then converged with the respective quantitative results and efficacy outcomes for synthesis. In phase 3, the interpretation of findings, we will seek to understand if and how our strategy worked, for who, and in what context.

Results

Recruitment and enrollment began in December 2020, and the first cohort of families will begin the intervention in March

2021. As of March 15, 2021, 10 children and their parents were enrolled in the study; however, intervention delivery had not begun. Future outcomes will be published in peer-reviewed health-related research journals and presented at national, regional, or state professional meetings and conferences. Preliminary findings will position the investigative team to design a subsequent hybrid study that will include a powered pilot randomized controlled trial with a larger sample of families and providers, a usual care control arm, and long-term follow-up; a robust evaluation of a refined implementation protocol; and cost-benefit and return-on-investment analyses.

Discussion

The TELE-GEN pilot trial will begin to address critical barriers to defining a gold standard lifestyle intervention for AA families with children at risk for T2DM. The proposed approach is supported by the scientific literature [33,123] and leverages existing infrastructure to engage AA parents in a virtual community, a context most relevant in response to the current COVID-19 global pandemic [124-127]. The proposed study aims and innovative hybrid research design will contribute to advancing translational research by optimizing clinical and implementation science to improve health and reduce disease occurrence [128]. The proposed intervention is also scalable given the current health care subsidies for telehealth interventions [51,129,130] and future subsidies emerging from telehealth demands resulting from the COVID-19 pandemic [124-127]. Finally, the proposed intervention could be feasibly disseminated, adapted, and implemented to treat obesity and prevent T2DM in high-risk AA pediatric populations throughout the United States.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

NIH Peer Review Summary Statement; 2019 COBRE submission.

[\[PDF File \(Adobe PDF File\), 336 KB - resprot_v10i3e25699_app1.pdf\]](#)

Multimedia Appendix 2

NIH Peer Review Summary Statements; COBRE Submission 2020.

[\[PDF File \(Adobe PDF File\), 126 KB - resprot_v10i3e25699_app2.pdf\]](#)

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Abbreviations

AA: African American

ADA: American Diabetes Association

DPP: Diabetes Prevention Program

HbA_{1c}: hemoglobin A_{1c}

PI: principal investigator

REDCap: Research Electronic Data Capture

T2DM: type 2 diabetes mellitus

TECH: Telehealth in Chronic Disease

TELE-GEN: Telehealth Diabetes Prevention Intervention for the Next Generation of African American Youth

UMMC: University of Mississippi Medical Center

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Protocol

Assessing the Mental Health of Emerging Adults Through a Mental Health App: Protocol for a Prospective Pilot Study

Asal Yunusova¹, BA; Jocelyn Lai¹, MA; Alexander P Rivera¹, BA; Sirui Hu^{2,3}; Sina Labbaf³, BSc; Amir M Rahmani^{3,4}, PhD; Nikil Dutt^{3,5,6}, PhD; Ramesh C Jain³, PhD; Jessica L Borelli¹, PhD

¹Department of Psychological Science, University of California, Irvine, Irvine, CA, United States

²Department of Economics, University of California, Irvine, Irvine, CA, United States

³Department of Computer Science, University of California, Irvine, Irvine, CA, United States

⁴School of Nursing, University of California, Irvine, Irvine, CA, United States

⁵Department of Electrical Engineering and Computer Science, University of California, Irvine, Irvine, CA, United States

⁶Department of Cognitive Sciences, University of California, Irvine, Irvine, CA, United States

Corresponding Author:

Jessica L Borelli, PhD

Department of Psychological Science

University of California, Irvine

4552 Social and Behavioral Sciences Gateway

Irvine, CA

United States

Phone: 1 9498243002

Email: Jessica.borelli@uci.edu

Abstract

Background: Individuals can experience different manifestations of the same psychological disorder. This underscores the need for a personalized model approach in the study of psychopathology. Emerging adulthood is a developmental phase wherein individuals are especially vulnerable to psychopathology. Given their exposure to repeated stressors and disruptions in routine, the emerging adult population is worthy of investigation.

Objective: In our prospective study, we aim to conduct multimodal assessments to determine the feasibility of an individualized approach for understanding the contextual factors of changes in daily affect, sleep, physiology, and activity. In other words, we aim to use event mining to predict changes in mental health.

Methods: We expect to have a final sample size of 20 participants. Recruited participants will be monitored for a period of time (ie, between 3 and 12 months). Participants will download the Personicle app on their smartphone to track their activities (eg, home events and cycling). They will also be given wearable sensor devices (ie, devices that monitor sleep, physiology, and physical activity), which are to be worn continuously. Participants will be asked to report on their daily moods and provide open-ended text responses on a weekly basis. Participants will be given a battery of questionnaires every 3 months.

Results: Our study has been approved by an institutional review board. The study is currently in the data collection phase. Due to the COVID-19 pandemic, the study was adjusted to allow for remote data collection and COVID-19–related stress assessments.

Conclusions: Our study will help advance research on individualized approaches to understanding health and well-being through multimodal systems. Our study will also demonstrate the benefit of using individualized approaches to study interrelations among stress, social relationships, technology, and mental health.

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KEYWORDS

ecological momentary assessment; stress; digital mental health; college student; mental health; protocol; prospective; feasibility; individual; factors; sleepy; physiology; activity; COVID-19

Introduction

Background

Chronic stress is associated with a person's physical and emotional well-being. In the United States, 4.7%-11.2% of adults regularly experience worry, anxiety, nervousness, or depression [1]. Stress is a major factor that may contribute to cardiovascular diseases (eg, stroke) [2,3], and repeated stress exposure is linked to adverse mental health outcomes and behaviors, such as depression, anxiety, self-harm, suicidality, and addiction [4,5]. Adolescence and young adulthood are at-risk periods of development wherein mental disorder and mortality incidence rates largely increase [6-9]. These changes in mental health may, in part, be due to rapid shifts in physical and psychological development during brain maturation [10-12]. Indeed, emerging adults, including college students, experience chronic stress; one-fifth of students meet the criteria for severe behavioral problems [13], approximately 30% of college students meet the criteria for depression [14], and 10% of students screen positively for anxiety disorder [15]. Students often experience increases in allostatic load due to continuous exams, the increased number of nonacademic responsibilities (eg, jobs), changes in social support (eg, moving away from home), social stressors (eg, making new friends), and other events that are associated with living in a new environment. These stressors are also accompanied by uncertainty and challenges to individuals' identities [16,17]. Given these academic, social, and psychological stressors, it is hardly surprising that universities struggle to meet the demand for on-campus mental health services [18]. Additionally, students who need mental health services the most may not take advantage of these services because of social stigma and pragmatic reasons (eg, time constraints) [18,19]. Therefore, stress reduction and management are crucial for this population, as they may experience high-intensity negative emotions [20]. Furthermore, emerging adults have yet to develop the maturity required for exerting top-down control over intense emotional experiences [21]. The goal of this paper is to introduce a research protocol for a prospective study that examines the feasibility of a multimodal approach to understanding the unique individual nuances of mental health.

Psychologists and human behavior researchers have long understood the importance of adaptive stress responses and emotional functioning in well-being. Understanding the intricacies of mental health and its associations with numerous physical and life behaviors is important for choosing interventions and approaches that promote good mental health. From this perspective, mental health is viewed along a health continuum, wherein individuals may fluctuate across a spectrum of diminishing and flourishing mental health [22]. Psychological functioning is closely associated with physical functioning; the manifestations of mental states may be apparent in a person's physical state [23]. For example, heart-rate variability (ie, a measure of the variation of time between heartbeats) is linked with the stress responses of individuals with affective disorders [24]. Furthermore, with regard to physiological signs and their relevance to mental health, sleep and physical activity are important factors that are associated with mental health [25,26].

Studies often examine these factors separately; sleep researchers may not account for physiological activation or activity, and physiology experts may not include measures of sleep in their studies. A crucial next step in the field of mental health research is examining the interconnectedness of these factors in real time to increase the ecological validity of mental health assessments. This can be done by taking advantage of advancements in technology that ultimately improve mental health treatments. Recent clinical studies have noted the utility of individualized approaches that address mental health concerns.

For several decades, research has focused on how different strategies for coping with stress or maladaptive emotional experiences (ie, feeling emotions too intensely, feeling emotions for too long, or feeling emotions in the wrong context) [27,28] relate to psychopathology and worsen health [29,30]. Typically, stress management for emotion and mood-related disorders include evidence-based treatments such as cognitive behavior therapy, acceptance and commitment therapy, and dialectical behavior therapy [31-33]. However, clinical researchers have suggested that more personalized models and approaches for understanding individual differences and individuals' unique experiences may inform research on the risk of developing psychopathology [34]. Recently, clinical research has focused on understanding the complexities of mental health symptoms within and around an individual [35]. Furthermore, clinical researchers have been increasingly using transdiagnostic and precision medicine approaches instead of relying on the typical clinical categories and diagnoses in the Diagnostic and Statistical Manual (DSM) [36-39]. This gradual shift from using the DSM is partially due to inconsistencies in clinical diagnoses (ie, symptoms of different disorders often overlap). More specifically, patients do not always exhibit the same symptoms for the same disorder. For instance, depression might impact an individual's sleep, but depression might manifest in the form of anhedonia or social withdrawal for other individuals. Furthermore, other clinical diagnoses, such as posttraumatic stress disorder, may result from differing types of trauma, which affect the type of symptoms that an individual might exhibit [40]. In addition, people with different diagnoses (eg, anxiety and depression) share many common features (eg, avoidance and withdrawal) and often benefit from the same or similar interventions (eg, exposure or behavioral activation). The recognition of heterogeneity in symptoms and clinical presentations within diagnostic categories, and the recognition of homogeneity across clinical groups has led many to question the utility of the DSM [37,39]. With the ongoing shift in clinical research, researchers have begun to use individualistic approaches for understanding the risks and development of psychopathology. Researchers have also questioned whether a personalized model of treatment that is based on the unique symptomatology of an individual would result in a more effective means of recovery. Furthermore, it is crucial to examine changes in symptoms and behavior over time.

Clinical researchers have begun to use personalized model approaches that take advantage of the advancement and use of wearable and mobile technology, which can be used to predict and prevent adverse mental health outcomes. Noninvasive wearable devices allow researchers to track features that are

relevant to mental health, such as mood, sleep, and physiology [41-44]. The use of intensive, longitudinal approaches (eg, daily reporting and the use of wearables) allows researchers to better understand the manifestations of psychopathologies and predict symptomatology [45-47]. For example, studies have combined subjective reporting for evaluating mood with objective measures for physical activity to understand the associations between negative mood and physical activity [48]. Moreover, researchers have recommended the use of individualized approaches for understanding psychopathology; treatments can be tailored to each individual, as a person's symptoms may differ from those of another person with the same psychopathology [34]. The Internet of Things (IoT) is a nascent, but rapidly growing paradigm wherein the objects of everyday life are equipped with sensing, processing, storage, communication, and networking capabilities that allow objects to communicate with each other and with users. These objects have become an integral part of the internet [49,50]. In addition, wearable devices (ie, smart wristbands, rings, clothing, etc) form a rapidly emerging new class of IoT technologies named wearable IoT (WIoT) technologies, which have the ability to sense critical physiological, behavioral, and contextual data. WIoT technologies can also analyze, store, and transmit these valuable data [51]. An artificial intelligence-enabled event mining system that operates on such rich big data can be used to assess temporal associations among events, for the purpose of building personalized models. These personalized models can be used to enhance the health and well-being of individuals. A personalized model approach allows researchers to conduct root cause analyses and study interrelations among stress, social relationships, technology, and mental health. To gain a holistic perspective of well-being and factors that contribute to fluctuations in one's mental health, researchers often use IoT technologies to monitor physical health (ie, sleep, physical activity, and physiology) and behaviors, and to conduct ecological assessments (eg, daily diaries and surveys) for assessing psychological well-being (ie, mood, emotion, and depression). An advantage of a holistic approach includes the ability to identify various environmental and social factors that may be overlooked during standardized diagnostic tests, since it is well known that psychological disorders do not have one root cause [52-54]. Although there are many benefits to using these approaches, a large portion of related literature has only focused on the theoretical advantages [55]. Many studies have yet to examine data that support these theoretical advantages. Indeed, holistic and personalized approaches are a recent, emerging topic in the field of psychology; researchers have used machine learning and network analysis techniques for analyzing intensive, self-reported assessment and wearable data, to examine symptom clusters for depression [56]. Furthermore, this approach may help with informing mental health interventions and health care providers' clinical recommendations. Studies on the IoT and the use of wearables in health monitoring have suggested that clinicians may be able to use WIoT technology-based information to complement their diagnoses and recommendations [57]. The recent advancements in WIoT technology research have allowed researchers to use personalized and holistic approaches for understanding the development of mood disorders.

Objective

In this protocol paper, we describe a prospective study that aims to assess the effectiveness of a multimodal approach for establishing a more comprehensive understanding of an individual's experience. We will achieve this by conducting subjective, behavioral, and physiological assessments. The use of WIoT technologies that capture in-the-moment experiences and contexts, such as the Oura ring and Samsung Gear Sport smartwatch, has been shown to improve the ecological validity of mental health assessments [58,59]. Thus, a goal of our prospective study is to use a multimodal assessment method that combines data from emerging WIoT technologies and personal chronicles in a daily activity logging framework (ie, the Personicle app) [60,61], to better understand the unique contexts and factors of stress and emotional well-being, as well as the risks and development of psychopathologies among young adults. More specifically, this study aims to investigate daily factors (ie, stressors and activities) and their relationship with the psychopathologies and daily emotions of college students. Ultimately, we believe that our study will help with developing personalized models that can be used to monitor, predict, and treat mental health and well-being issues among emerging adults. Specifically, we test the following big-picture research question: is it possible to build personalized predictive models of mental health for individuals? For example, sleep disturbances and poor social interaction skills can be used as factors for predicting increases in depression severity. However, reduced amounts of physical activity and low positive emotionality are other factors that can be used to predict increases in depression severity over time.

We believe that the methods we describe in this protocol paper may allow psychologists to identify the root causes of stress and develop an evidence-based approach for monitoring stress and emotions among adolescents and young adults. Herein, we provide an overview of our prospective study.

Methods

Study Design

Eligibility Criteria and Recruitment

Our protocol was approved by the institutional review board at the University of California, Irvine (approval number: 2019-5153). We will recruit participants by distributing flyers throughout the college campus community, disseminating related digital content on social media pages (ie, the University of California, Irvine Facebook pages), sending emails to people on the university listservs, and telling members of the teaching faculty to share study information on their class websites. These methods will hopefully yield a broad and representative sample of college students across different disciplines and years of study. Eligible participants include full-time students from the University of California, Irvine aged 18-22 years, and those who own an Android smartphone (ie, must be students' primary phone) that is compatible with the Personicle app, ecological momentary assessment (EMA) phone-based surveys, and study devices. Participants are ineligible if they are parents, are married, are returning to school after a period of ≥ 3 years, or



are unable to speak/write English fluently. Eligibility will be determined via email and phone screening, which will be conducted prior to laboratory visits. Participants with indications of suicidal ideation or moderate to severe depression during the survey assessments will undergo additional screening, which will be conducted by one of the lead researchers (ie, JB, a clinical psychologist). The lead researcher may decide to withdraw participants from the study to protect participants' safety and health. This strategy will ensure that participants with mental health concerns (eg, depression) will still have the opportunity to participate in the study.

Data Collection Procedures

Our study will involve an in-lab preassessment, followed by a 12-week remote data collection period and an in-lab exit assessment. During the preassessment, participants will fill out a consent form and complete a questionnaire battery that consists of standard psychological and relationship-based measures. Demographic information, including age, year of schooling, gender, ethnicity, and relationship duration, will be collected. After the preassessment, participants will be given noninvasive WIoT devices that assess activity and physiology throughout the day and during sleep, in an effort to capture an accurate depiction of participants' daily physical habits and health (see [Figure 1](#)). Participants will then be asked to download four apps onto their smartphone; one app will be for completing daily surveys on emotion, the second app (ie, Personicle) will collect daily activity data (eg, phone interactions and physical activities), and two others (Oura and Galaxy wearable) in order to use the wearables and track the data. At the end of the 12-week period, participants will complete a battery of questionnaires, which will be similar to their initial assessment battery. At the end of their participation, participants will complete a final, postassessment questionnaire that contains

additional questions about technology acceptance, open-ended feedback, and whether they used mental health services during the participation period. Participants will be told to wear their smart devices at all times (ie, if possible) and sync their devices every few days, to ensure that our servers receive the data. Participants will also be informed that they need to maintain a survey completion rate of at least 80%. This percentage was chosen based on previous research studies that required a similar completion rate [62,63]. To maintain high adherence rates and low attrition rates, we will monitor incoming data on a weekly basis to ensure that participants are syncing and wearing their devices and completing the daily survey. Our web-based dashboard provides real-time information on the wear time of sensors and the completion status of surveys. Participants will be contacted if they fall below the weekly 80% assessment completion rate. Participants will also be sent reminders via text message, email, or phone call if more than 2-3 days of inactivity per week are detected. Inactivity will be defined as failing to sync the ring or watch, failing to wear the ring or watch, and failing to complete the daily and weekly survey. Reminders will be primarily sent via text message, but if participants do not respond or do not adhere to study procedures, then the research team will send reminders via email and phone call. We will set up a study-specific Gmail account and Google voice account for contacting participants. The reminders will state something to the effect of the following: "Hello, we have noticed that you have not completed the daily survey within the past 2 days. Your survey completion rate is currently at 70%. To ensure you are completing at least 80% of the surveys, please remember to complete the survey every day." Furthermore, the reminders will be administered on a case-by-case basis, because survey completion is influenced by external factors, such as the survey app not functioning on a certain day or a wearable device being faulty.

Figure 1. Data that are collected by the Oura ring and the Samsung Gear Sport smartwatch. The Oura ring collects data on sleep, readiness, and activity. The Samsung Gear Sport smartwatch collects data on sleep and activity, by using sensors (ie, a barometer) and a pedometer system.

Oura Ring	Samsung Gear Sport
	
<p><u>Sleep Variables</u></p> <ul style="list-style-type: none"> • Sleep Score • Sleep Stage Guidance • Total Sleep Time (Rem, Light, Deep) • Total Awake Time • Sleep Latency • Sleep Efficiency • Lowest Resting Heart Rate <p><u>Readiness Variables</u></p> <ul style="list-style-type: none"> • Readiness Score • Night Time Resting Heart Rate • Nighttime Heart Rate Variability • Nighttime Body Temperature • Nighttime Respiratory Rate • Heart Rate Variability (Hrv) Balance • Restful Moments • Recovery Index • Sleep Balance • Activity Balance <p><u>Activity Variables</u></p> <ul style="list-style-type: none"> • Activity Score • Activity Goal Progress • Total Burn • Walking Equivalency • Steps • Training Frequency • Training Volume • Daily Movement 	<p><u>Sensors:</u></p> <ul style="list-style-type: none"> • Accl • Gyro Sensor • Barometer • Photoplethysmogram (PPG) • GPS <p><u>Pedometer System</u></p> <ul style="list-style-type: none"> • Walking Steps • Running Steps • Moving Distance • Calories Burnt • Last Speed • Last Stepping Frequency <p><u>Sleep Variables</u></p> <ul style="list-style-type: none"> • Total Sleep Time (Rem, Light, Deep) • Total Awake Time • Sleep Latency • Sleep Efficiency

Mental Health and Well-Being Assessment Battery

At study intake and at regular intervals thereafter (ie, 3 months following intake and every 3 months after that point), participants will complete a mental health and well-being assessment battery. This battery will be identical at each time point (with the exception of additional measures at the follow-up and postassessment), and will contain a variety of validated, gold-standard assessment tools that are used for measuring an array of mental health symptoms that are common in the emerging adult population. The assessments that the participants will complete include (1) the 21-item Beck Depression Inventory-II [64], which measures the severity of the cognitive, affective, behavioral, and physiological symptoms of depression that people experience over 2 weeks; (2) the 6-item anxiety subscale of the Brief Symptom Inventory [65], in which anxiety severity is rated on a 4-point subscale that ranges from 0 (ie, not at all) to 4 (ie, extremely); (3) the 3-item University of California, Los Angeles Loneliness Scale [66], in which loneliness is rated on a Likert scale that ranges from 1 to 3; and (4) the Brief Coping Orientation to Problems Experienced Scale, which is a 28-item questionnaire on coping responses (eg, substance abuse) for stressful events [67]. At the end of the study, participants will complete one final mental health and well-being assessment battery. With regard to the scales in this battery, we will calculate the internal consistency of each

measure and compute participants' total scores for each measure. Multiple assessments of participants' mental health and well-being data, and identical measures across time intervals will enable us to examine changes in mental health and well-being indicators across the year.

Wearable Devices

Oura Ring

The Oura ring [68] measures a myriad of physiological variables, which are categorized into three general health areas, as summarized in Figure 1. The Oura ring collects information on sleep, including the time that participants spend in different stages of sleep (ie, the light, deep, and rapid eye movement stages), by detecting and interpreting physiological measures such as heart rate, heart rate variability, and pulse wave variability amplitude [69,70]. The Oura ring will uniquely calculate participants' activity variables, including energy expenditure and activity level, based on a highly personalized combination of body metrics (ie, height, weight, age, and gender) and 3D accelerometer data. Metabolic equivalents [71] are the Oura ring's primary unit for measuring energy expenditure. These are taken into consideration when the Oura ring categorizes the intensity of aerobic exercise. Additionally, each participant will be given a personalized activity score on each day. Activity scores reflect participants' overall activity intensity, activity frequency, and postworkout recovery time.

Participants will be given the opportunity to view their data (eg, the weekly trends of each measure) on the Oura app (Figure 2), which participants will install on their phones during the initial assessment session.

Figure 2. Examples of Oura ring screens that display information on heart rate variability, daily movement, and sleep stages. These screens can be viewed on the Oura phone app.

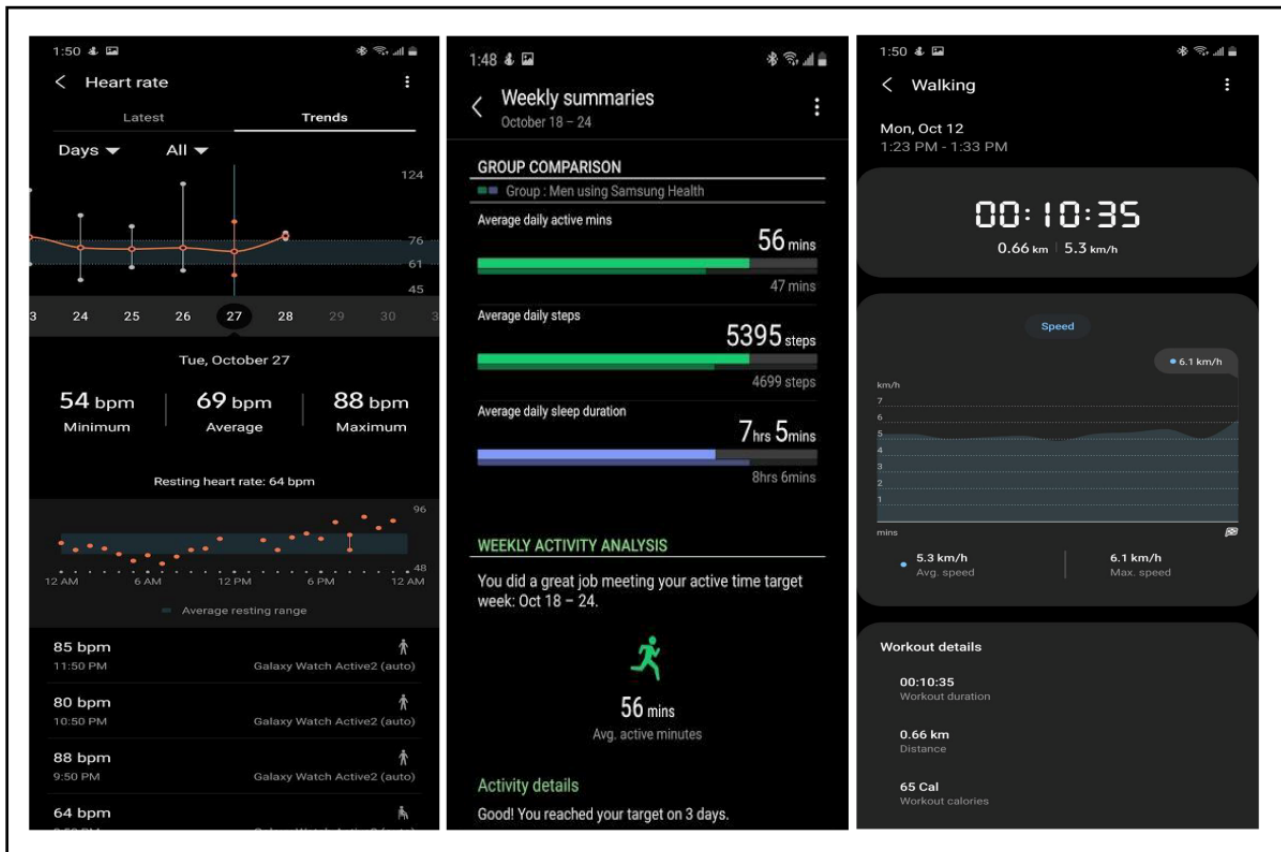


Samsung Gear Sport Smartwatch

In addition to the Oura ring, participants will be given a Samsung Gear Sport smartwatch to wear on a daily basis. The Samsung Gear Sport smartwatch operates on the open-source Tizen Operating System, includes open software development kits, and provides open access to raw signals [72]. The smartwatch's sensors measure vital signs and signals, such as photoplethysmogram signals, heart rate, heart rate variability, and respiration rate. This allows the smartwatch to assess stress, activity levels, and sleep (see Figures 1 and 3). Furthermore, our research team has developed an app that can be used on this watch. The app extracts raw signals (eg, photoplethysmogram and proper acceleration signals) from the watch's sensors, which

allows us to conduct elaborate biosignal processing and machine learning analyses on data, and to assess complicated phenomena, such as stress. Similar to the Oura ring, the Samsung Gear Sport smartwatch uses a variety of sensors to quantify different activity habits (Figure 1). The watch places a heavy emphasis on exercise and activity metrics, and unlike the Oura ring, the watch uses a gyroscope and altimeter to assess environmental factors, such as altitude and step incline, for calculating variables such as the number of calories burned and moving distance. When paired with the Oura ring, the Samsung Gear Sport smartwatch provides a sensory system that yields an all-encompassing insight into the exercise and activity habits of the participants.

Figure 3. Examples of Samsung Gear Sport activity screens that display cycling information (eg, trends, speed, heart rate, and elevation). These screens can be viewed on the Galaxy Wearable phone app.

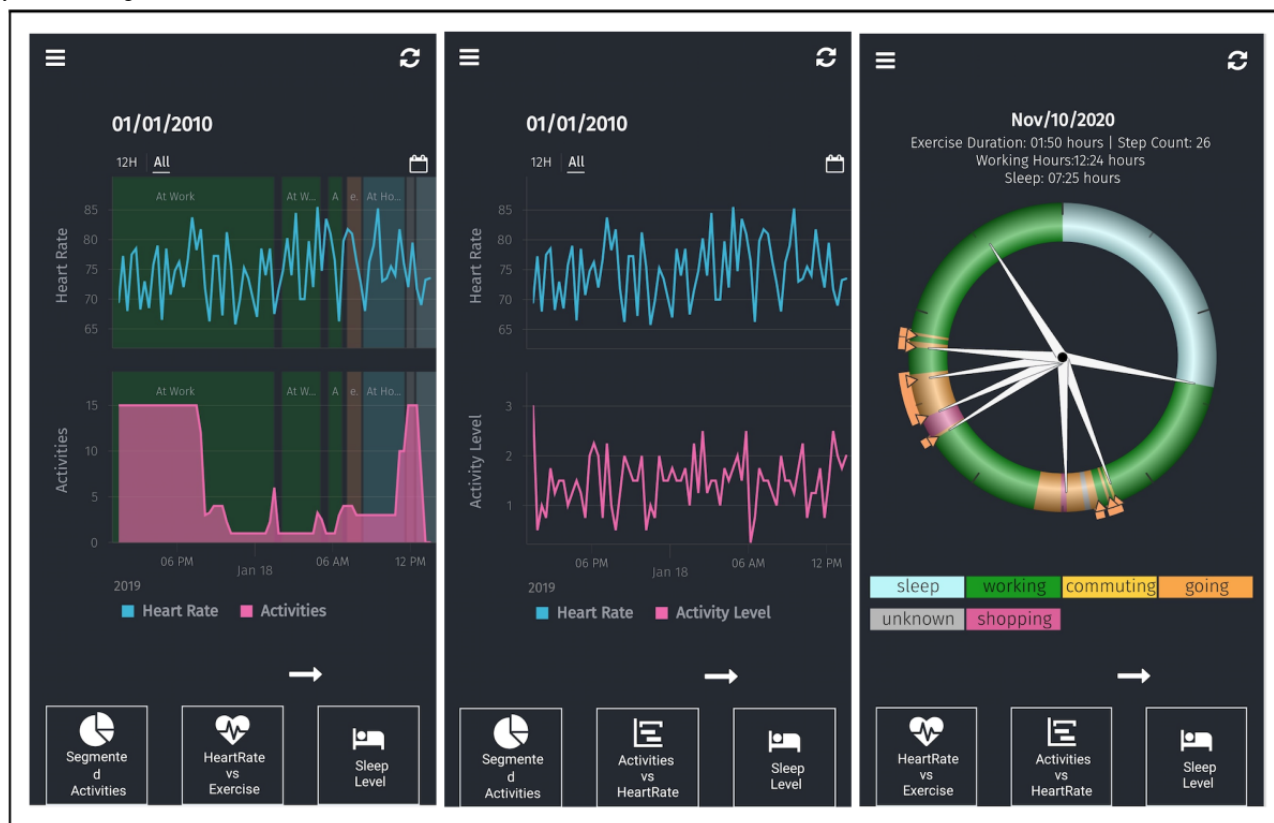


Personicle App

Personicle is a multimodal personal chronicle of daily activity that automatically integrates heterogeneous sensory data from the IoT (eg, accelerometer, gyroscope, altimeter, GPS, light sensor, and temperature sensor) with contextual, social, and environmental information to create a chronicle of life events (ie, activities and biomarkers) [60,61]. For the purpose of our study, the Personicle app will be used to assess the three following main event categories: activity-related (eg, walking and socializing), health-related (eg, high heart rate variability), and context-related (eg, stressful workplace, parents' house and friend's house) events (see Figure 4). To identify daily activities, we built a common daily activity model by identifying the global unique properties of each individual event. Specifically, we used a common event modeling approach to analyze the physical

(eg, event occurrence time stamps and intervals), logical (eg, temporal domain), and relative (eg, temporal relationships to other events) relationships between each aspect and an event. We incorporated these general aspects into the categories of our modeling attributes and modified the physical, logical, and relative components to match those of daily activities. We developed an event mining system to identify temporal associations among events, which allowed us to build personalized models [73]. For instance, to understand an individual's social behavior, we must examine their locations (eg, the amount of time an individual spends at various places, such as a friend's home or parents' home). We also used our event mining system to identify linkages between activities (eg, going out for ice cream) and behaviors (eg, driving to friend's house), which also contribute to building an individual's personalized model.

Figure 4. Examples of screens that are shown on the Personicle phone app. These screens display information on physical activity (eg, heart rate) and daily activities (eg, home events).



Daily and Weekly Assessments

Participants' daily moods will be assessed by using the Positive and Negative Affect Schedule [74], which is a validated measure for assessing both positive and negative affect (ie, inspired, excited, distressed, and upset). The Positive and Negative Affect Schedule is presented as a slide scale with indicators at the top ranging from “very slightly” (0) to “extremely” (100). Emotion

assessments will be evaluated with one of the phone apps that participants will install onto their smartphones (see Figure 5). Participants will also answer two open-ended response questions once a week, to provide additional context for their subjective experiences (ie, “Please write about your high points and low points this week. Please try to be as detailed as possible” and “Please rate how you felt about your week”).

Figure 5. An example of the daily assessment surveys that participants are instructed to complete every evening.

PERSONICLE QUESTIONS

Indicate the extent you have felt this way today

Very slightly A little Moderately Quite a bit Extremely

Interested

Distressed

Excited

Upset

Strong

Guilty

Scared

Hostile

Data Analytic Plan

Since our pilot study aims to assess the feasibility of using an extensive multimodal approach for understanding the holistic aspects of stress and well-being, our analyses are exploratory in nature. Furthermore, our sample size is small. Thus, we will take into account the adherence rate and the amount of collected data during the assessment period. We will contact participants throughout the data collection process in order to maintain an estimated adherence rate of 80% and reduce the amount of missing data. However, missing data will be reviewed and imputed via full-information maximum likelihood estimation, based on the assessments that participants have completed on other days. Since the questionnaire will be conducted at multiple time points throughout the study, we intend to examine whether there were changes in students' assessments of depression, loneliness, and well-being. More specifically, daily mood assessments will be based on participants' daily surveys; and daily physiology, sleep, and activity assessments will be based on the data collected from wearable devices. The wearables will allow us to assess physiology and activity at different time points throughout the day. To make these data comparable with those of our daily assessments (ie, assessments that are only conducted once during the day), we intend to aggregate these data to obtain a single value for each day. To examine associations between intensive longitudinal assessment data (ie, data that are collected daily over several months, including daily reported mood and sleep), we will conduct multilevel modeling analyses [75] to account for the multiple assessments of each individual. Time series analysis and dynamic multilevel modeling techniques are

common approaches to analyzing intensive longitudinal data and examining temporal associations and trajectories between constructs of interest [76]. However, given our intended sample size of 20 participants, our study design may be underpowered in terms of detecting an effect.

A central aim of our study is to examine the links among daily variables (eg, sleep, physiology, emotion, and Personicle data) and long-term mental health and well-being data. In order to achieve this aim, we will use data reduction strategies. For instance, we are collecting data on a broad battery of mental health and well-being scales in order to obtain a comprehensive assessment of participants' psychological functioning. By conducting an exploratory factor analysis, we will be able to examine whether these measures load onto underlying factors (eg, mental health, internalizing, and externalizing symptoms), and reduce the number of analyses we need to conduct. Furthermore, we will use multilevel modeling techniques to examine whether repeated measures data (eg, sleep, emotion, physiology) can be used to predict changes in mental health and well-being data.

In addition to the use of multilevel modeling approaches for examining associations among assessments over time at the within-person level, we intend to use idiographic and network analytic approaches for examining personalized models of mental health. Researchers have long used unified structural equation modeling (SEM) and dynamic SEM to create idiographic personalized models of personality and mental health [77,78]. Unified SEM is particularly helpful because it uses the group iterative multiple model estimation approach to

identify components of symptoms and associations among constructs within an individual. These data can be used to examine similarities across the sample [79,80]. Furthermore, network analyses that are conducted by using a multivariate time series analysis approach may also offer better insight into key psychopathology symptoms that an individual experiences [81,82]. Despite the small sample size and the possibility of participants withdrawing from the study, we will have numerous observations for each individual over the course of 12 months (ie, an estimated 3000-5675 observations in total). Thus, we will use multilevel modeling to assess the relationships among an individual's daily emotions, activities, and sleep patterns at the within-person level. We may be able to examine individual cases, wherein the relationships among an individual's emotions, activity, and sleep patterns may differ from those of another individual. For example, daily negative affect and poor sleep quality may be strongly related for one participant, whereas daily positive affect and increased activity levels may be strongly related for another participant.

Results

We expect 20 participants to complete the study. We recruited an initial cohort of participants between January 2020 and March 2020 (N=10), and they are expected to complete the 12-week data collection period and the following 9-month extension period. Due to the unexpected COVID-19 pandemic, we will make subsequent adjustments and additions to our study. We will change the consent form process and initial survey assessments so that they can be administered and completed via internet-based methods. We will also develop a procedure that will enable us to mail study devices to participants' homes. A research assistant will help participants set up the devices via video call. Furthermore, COVID-19-related questionnaire measures will be added to the battery questionnaire and daily survey, to assess the pandemic's psychological impact on participants. Due to the COVID-19 pandemic, participants will be offered to participate in an extension of the study, which will prolong their participation period by up to 9 months. During this extension period, participants will continue to undergo the same study procedures and complete follow-up assessment questionnaires every 3 months. To reduce attrition rates and increase adherence rates, participants' compensation will be increased for the additional months of participation. Research assistants will send participants encouraging reminders about the potential importance of our study, in order to underscore the fact that their participation is an important contribution to research. In doing so, we hope to incentivize participant adherence. Thus, we aimed to recruit a second cohort (N=10) during the months of June and July 2020. This cohort will be expected to participate in our study until the end of the year. Given that we will be analyzing participant data over the span of a year, there may be certain time points in which participants may encounter challenges to completing the daily assessments of the study. We recognize that there may be periods of time wherein we miss large amounts of data. We hope that by closely focusing on periods of time (ie, over a 3-month span) and specific events (ie, the start of the shelter-in-place during the pandemic, and before and after the US presidential election),

we will be able to examine participant data over long periods of time and reduce the amount of missing data.

The use of wearable sensors for 12 months comes with the inevitable issue of missing data. Our group has devised a multitier strategy to mitigate the amount of missing sensory data. Our study uses a multimodal data collection process that involves the long-term aggregation of data from several sources. Even though several challenges arise when implementing and managing such a process, we believe that a by-product of this process is inherent data resiliency, which will enable us to apply data imputation techniques for minimizing the amount missing data. The main reasons for missing data include the following: (1) a user is unable or not willing to wear the device for several periods of time; (2) the device runs out of battery power for a period of time; (3) device failure occurs; or (4) the device is momentarily detached from the body. These may result different forms of missing data, as follows: (1) missing completely at random data, which include data that are missed due to sensor failure; (2) missing at random data, which include data that are missed because the device is detached from the body (eg, times when the device is charging); and (3) not missing at random data, which include data that are missed when a user removes the device (eg, before smoking) to hide an activity's effect on vital signs. We will use well-accepted data imputation techniques, such as deletion methods (eg, listwise or pairwise deletion), multiple imputation methods, model-based methods (eg, direct maximum likelihood estimation), machine learning-based methods, and multisource methods, based on the type of missing data. Our criteria for selecting data imputation techniques include (1) unbiased parameter estimates; (2) acceptable estimates of variability (ie, correct standard errors); and (3) the highest statistical power. We will also use a technique that was recently proposed by our group; this involves a missing data-resilient, decision-making, personalized approach for assessing health care IoT devices [83]. This method has been validated in an 8-month continuous maternity care project [84].

In summary, we will take advantage of the multimodality nature of two separate wearables (ie, sensory inputs, personalization, and the redundancy of different signals), to perform advanced data imputation techniques for recovering missing data or mitigating the amount of missing data. Furthermore, a web-based dashboard will assist the research team in the early identification of technical issues during monitoring. The research team will also receive alerts about the occurrence of missing data (eg, users not wearing the sensors for a period of time, the research team not receiving data packets due to internet connection issues, etc).

Discussion

Contributions

To our knowledge, ours is one of the first studies to use EMA surveys, wearable smart devices, and a personal event life logging system to record daily moods and events to build a personalized model for predicting changes in the mental health and well-being of college students. A strength of our ongoing study is that we have an immense amount of rich data from

participants that have been analyzed on a daily basis over the course of 1 year. Our study is also unique because we collected data before the COVID-19 pandemic and during the pandemic. This provided us with the opportunity to analyze patterns in everyday life during a pandemic. Furthermore, due to the COVID-19 pandemic, students face the challenge of using remote methods to maintain social relationships and complete coursework. This will further exacerbate well-being issues among college students [85,86]. Thus, our study has the ability to examine well-being patterns among college students that use remote learning methods during the pandemic. Additionally, the results of our pilot study will help Personicle become a better open-source IoT app that is available to the public.

Limitations

We anticipate that our study will have limitations that are similar to those of many other EMA-based studies, such as nonadherence to study procedures and experimental fatigue. These limitations might result in missing data [87]. Furthermore, participant burden may be reflected by the data quality of completion times for daily surveys (ie, taking time to select answers vs carelessly selecting answers), and biased responses (ie, the influence of the research team sending reminders and conducting follow-up examinations). Longitudinal studies may also have unintended effects, such as participants engaging in healthier behaviors when tracking their own emotions and health [88]. Despite these limitations, WIoT devices allow for naturalistic data collection processes that reduce the burden on participants. We also attempted to reduce participant burden by keeping daily assessments brief. Furthermore, participants who fail to meet our criteria for adherence rate (ie, participants with a weekly assessment completion rate of only 10%) will be withdrawn from the study. We will recruit additional participants to achieve our target sample size (ie, N=20), and keep careful records about the replacement of participants. As we are assessing college students over the course of a year, we may be able to include time as a covariate for examining changes in well-being over time (eg, changes in sleep patterns or physical activity over time). Additionally, several of the biggest limiting factors of the Personicle app include its general definitions for activities, its inability to collect data on a wide range of events, and its inability to distinguish specific events from a large segment of events.

Since the existing Personicle system was modified for our specific study, we expect that multiple system updates will be implemented to fix bugs and other issues. Although the refinement of the system may provide us with more accurate data, it might lower the accuracy and interpretability of previously collected data. We expect the need to notify enrolled participants about updating their Personicle app to the most recent version if updates do occur over the course of the study. However, a benefit of the Personicle system is that it allows users to send Personicle system logs (ie, files that have all the data that the app has collected) directly to the server. This will allow the research team to identify missing data or issues.

Another limitation is that our study began in January, with the intention of assessing students over the course of a certain period of time. However, since the COVID-19 pandemic has disrupted the daily lives of many individuals, our research plans had to be adjusted to account for participants' experiences during a pandemic. To study the impact of the pandemic, we incorporated additional questions into the daily assessments (ie, "Please rate how worried you felt about your health today" and "How worried were you about contracting COVID-19 today"). Participants will answer these questions by using a sliding scale that ranges from 0 (ie, not worried at all) to 100 (ie, extremely worried). Despite these changes, the amount of data that we collected over the course of the year and the COVID-19 pandemic offers potentially interesting insight into individualized experiences and well-being.

Conclusion

In the context of an individualized approach to understanding mental health and well-being, using WIoT devices and the Personicle app as a multimodal system allows us to conduct root cause analyses and study interrelations among stress, social relationships, technology, and mental health. Our study will provide fundamental contributions to the field of computing, as we investigate a holistic, cybernetic, closed-loop architecture for personalized model generation. Our study will also contribute to psychological science, as we have created an evidence-based approach based on individualized, Personicle-generated feedback for reducing stress and negative emotionality in adolescents and young adults.

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Conflicts of Interest

None declared.

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Abbreviations

- DSM:** Diagnostic and Statistical Manual
- EMA:** ecological momentary assessment
- IoT:** Internet of Things
- SEM:** structural equation modeling
- WIoT:** wearable Internet of Things

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Protocol

Impact of Intersecting Systems of Oppression on Diabetic Retinopathy Screening Among Those Who Identify as Women of Low Socioeconomic Status: Protocol for a Convergent Mixed Methods Study

Aleksandra Stanimirovic^{1,2,3,4,5}, BSc, MA, PhD; Troy Francis^{1,2,3,5}, BSc, MSc; Anna Cooper Reed³, MSW; Sonia Meeral^{1,2,5,6,7}, MSW; Olivera Sutakovic^{4,8}, MD; Rebecca Merritt⁹, BA; Michael Brent^{4,8}, MD; Valeria Rac^{1,2,3,4,5}, MD, PhD

¹Program for Health System and Technology Evaluation, Toronto General Hospital Research Institute, University Health Network, Toronto, ON, Canada

²Ted Rogers Centre for Heart Research at Peter Munk Cardiac Centre, Toronto General Hospital Research Institute, University Health Network, Toronto, ON, Canada

³Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada

⁴Diabetes Action Canada, CIHR SPOR Network, Toronto, ON, Canada

⁵Toronto Health Economics and Technology Assessment Collaborative, Toronto General Hospital Research Institute, University Health Network, Toronto, ON, Canada

⁶Gender, Feminist & Women Studies, Faculty of Graduate Studies, York University, Toronto, ON, Canada

⁷Lyle S Hallman Faculty of Social Work, Wilfrid Laurier University, Brantford, ON, Canada

⁸Department of Ophthalmology, Toronto Western Hospital, Toronto, ON, Canada

⁹South Riverdale Community Health Centre, Toronto, ON, Canada

Corresponding Author:

Valeria Rac, MD, PhD

Ted Rogers Centre for Heart Research at Peter Munk Cardiac Centre

Toronto General Hospital Research Institute

University Health Network

200 Elizabeth Street

Toronto, ON

Canada

Phone: 1 416 634 8799

Email: valeria.rac@theta.utoronto.ca

Abstract

Background: By 2025, 5 million Canadians will be diagnosed with diabetes, and women from lower socioeconomic groups will likely account for most new diagnoses. Diabetic retinopathy is a primary vision complication of diabetes and a leading cause of blindness among adults, with 26% prevalence among women. Tele-retina is a branch of telemedicine that delivers eye care remotely. Screening for diabetic retinopathy has great potential to reduce the incidence of blindness, yet there is an adverse association among screening, income, and gender.

Objective: We aim to explore gender disparity in the provision of tele-retina program services for diabetic retinopathy screening in a cohort of women of low socioeconomic status (SES) receiving services in South Riverdale Community Health Centre (SRCHC) between 2014 and 2019.

Methods: Using a convergent mixed methods design, we want to understand patients', providers', administrators', and decision makers' perceptions of the facilitators and barriers associated with the implementation and adoption of tele-retina. Multivariate logistic regression will be utilized to assess the association among client characteristics, referral source, and diabetic retinopathy screening. Guided by a grounded theory approach, systematic coding of data and thematic analysis will be utilized to identify key facilitators and barriers to the implementation and adoption of tele-retina.

Results: For the quantitative component, we anticipate a cohort of 2500 patients, and we expect to collect data on the overall patterns of tele-retina program use, including descriptions of program utilization rates (such as data on received and completed diabetic retinopathy screening referrals) along the landscape of patient populations receiving these services. For the qualitative

component, we plan to interview up to 21 patients and 14 providers, administrators, and decision makers, and to conduct up to 14 hours of observations alongside review of relevant documents. The interview guide is being developed in collaboration with our patient partners. Through the use of mixed methods research, the inquiry will be approached from different perspectives. Mixed methods will guide us in combining the rich subjective insights on complex realities from qualitative inquiry with the standard generalizable data that will be generated through quantitative research. The study is under review by the University Health Network Research Ethics Board (19-5628). We expect to begin recruitment in winter 2021.

Conclusions: In Ontario, the screening rate for diabetic retinopathy among low income groups remains below 65%. Understanding the facilitators and barriers to diabetic retinopathy screening may be a prerequisite in the development of a successful screening program. This study is the first Ontario study to focus on diabetic retinopathy screening practices in women of low SES, with the aim to improve their health outcomes and revolutionize access to quality care.

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KEYWORDS

gender; screening; diabetes; diabetic retinopathy; blindness; technology; tele-retina screening; health equity; intersectionality theory

Introduction

Social and Economic Impacts of Diabetes and Its Complications

Diabetes is a significant public health burden, affecting 382 million people worldwide [1]. In Canada, the prevalence was estimated at 3.4 million (9.3%) in 2015 and is expected to increase to 5 million (12.1%) by 2025 [2]. Diabetic retinopathy is the primary vision complication caused by diabetes [3] and is the leading cause of new cases of blindness in adults aged 20 to 65 years [4]. The prevalence of diabetic retinopathy in Canada ranges from 20% to 30% [4]. Over a million people from Ontario were affected by diabetic retinopathy in 2016 [5]. Among Canadian adults, 5.7% have visual impairments with a variation in the provincial prevalence of visual impairment from 2.4% in Manitoba to a staggering 10.9% in Newfoundland and Labrador [6]. Lower income and type 2 diabetes have been shown to be associated with increased odds of visual impairment [6].

One-third of adult diabetic patients did not receive an eye examination for diabetic retinopathy within 2 years [5], and more specifically, 25.3% of people with diabetes over the age of 60 years had not seen an eye care provider in the last year [7]. The prevalence of vision loss in Canada is expected to increase nearly 30% in the next decade [8]. The financial implication of vision loss in Canada in 2007 was estimated to be CAD \$15.8 billion per annum, with CAD \$8.6 billion (54.6%) associated with direct health system expenditure; CAD \$4.4 billion (28.0%) associated with productivity loss resulting from lower employment, higher absenteeism, and premature death of Canadians with vision loss; CAD \$1.8 billion (11.1%) associated with costs to society created by market inefficiency from transfers including welfare payments and taxation forgone; CAD \$0.7 billion (4.4%) associated with the value for the care of people with vision loss; and CAD \$305 million (1.9%) associated with other indirect costs such as aids, home modifications, and funeral costs [9]. The value of the lost well-being (inclusive of disability and premature death) was estimated at CAD \$11.7 billion. In per capita terms, this adds

to a financial cost of CAD \$19,370 per person with vision loss per annum, and considering the value of lost well-being, the cost is CAD \$33,704 per person per annum [9]. The Canadian National Institute for the Blind (CNIB) estimated costs of associated complications of vision loss are as follows: falls, CAD \$25.8 million; depression, CAD \$175.2 million; hip fractures, CAD \$101.7 million; and nursing home admission, CAD \$713.6 million [10]. The National Coalition for Vision Health noted that health care costs for vision loss in Canada have been projected to increase to CAD \$30.3 billion per year by 2032 [11].

Health Disparities in Diabetes and Its Complications and Comorbidities

Health disparities in diabetes and its complications exist globally [12]. In Canada, ethnic minorities and Indigenous populations have a higher prevalence of diabetes than nonminority populations [13]. Diabetes appears to be more common among men than women. Socioeconomic status (SES) is inversely related to the prevalence of diabetes, but income-related disparities are greater among women [13]. In comparison to men with diabetes, women were more likely to be in the lowest income quintiles than the highest [14]. The odds ratio of developing diabetes doubles in men and almost triples in women in the lowest income category compared with those in the highest income category [15], and among Aboriginal Canadians, two-thirds (66.6%) of diagnosed individuals are women [16]. The Project for an Ontario Women's Health Evidence-based Report (POWER) study found that women of lower SES with diabetes had worse health and functional statuses than men and stressed the importance of addressing gender differences, which may interfere with diabetes self-care among the general diabetic population [14]. In 2016, 1.8 million Canadian males and 2.2 million females aged 45 to 85 years experienced vision loss. Prevalence increased from 8.7% to 16.9% between 2011 and 2016 [17]. Prevalence proportions increased with age but decreased exponentially with the severity of impairment, and vision loss remains more common among females [17].

An adverse association between screening and income has been found previously. A published report indicated that women of

lower SES may not be screened for breast, lung, and colorectal cancers [3]. In fact, they may not have symptoms recognized early or receive the most effective treatment. Similar to cancer screening, diabetic retinopathy screening is essential for the early detection and treatment of diabetes-related visual impairments and blindness [18]. Yet, it is commonly underutilized among women of lower SES [18]. Because diabetic morbidity and mortality are associated with low SES, the need to address socioeconomic barriers for women must take precedence over simply ensuring the provision of diabetes medical management. This is the first Ontario study to focus on diabetic retinopathy screening practices in women of low SES, with great potential to improve their health outcomes and access to quality care.

Tele-Retina Screening for Diabetic Retinopathy

There are disparities in eye care utilization among community-dwelling Canadians, where eye care utilization is defined as the self-report of a visit to an optometrist or ophthalmologist in the past 12 months [7]. Of concern, 25.3% of people with diabetes above the age of 60 years had not seen an eye care provider in the last year. Men in comparison to women and people with lower income (linear trend $P < .05$) were less likely to use eye care [7].

Tele-retina is one of the diabetic retinopathy screening modalities. It is focused on reducing eye care disparities that lead to avoidable vision loss. Tele-retina is a branch of telemedicine that delivers eye care remotely. Retinal images and data are collected and transferred via telecommunication technology to eye specialists [19]. In many developing countries, tele-retina has been utilized to provide quality eye care to the underserved urban population and the unserved remote rural population [19]. Alternatives to in-person examinations, such as tele-retina, can triage patients to proper levels of care and reduce barriers to specialized eye care [19]. Screening and detection of diabetic retinopathy are important to reduce the incidence of blindness, as they can detect early sight-threatening lesions, which can be treated effectively. Factors contributing to patients' missed opportunities in access to timely treatment can include limited number of specialists and challenges related to time and travel.

The eye care pathway does not end with diabetic retinopathy screening. Individuals who are screened and those who remain unscreened and develop severe vision loss have access to comprehensive vision rehabilitation services. In Canada, comprehensive vision rehabilitation represents a multidisciplinary pathway that encompasses the full spectrum of a patient's rehabilitation journey after vision loss, from initial assessment through intensive rehabilitation therapy [19].

Of note, in this study, tele-retina was utilized in an urban setting. It is also being utilized in rural settings such as First Nations reserves. It has the potential to scale to many rural communities that are underserved with respect to diabetic retinopathy screening and could be used as a strategy in conjunction with the Medical Mobile Care Unit (known as the CNIB Eye Van). The CNIB Eye Van is a fully equipped medical mobile eye care clinic that travels (with an ophthalmologist on board) to patients in Northern Ontario, from March through

October each year [20,21]. The CNIB Eye Van was cancelled in 2020 owing to the COVID-19 pandemic, leaving patients without care. A tele-retina program is a viable option that could address the needs of these patients.

Conceptual Frameworks

The Conceptual Social Determinants of Health framework adapted from the World Health Organization, Danaher framework, and Multi-Construct Intersectionality framework (Synergies of Oppression) will provide theoretical insights into the potential facilitators and barriers of the implementation and adoption of tele-retina screening for diabetic retinopathy. The frameworks will be used as analytical lenses to assess the system-, organizational-, and patient/provider-level causal factors of the tele-retina program. This approach will provide in-depth insights into the experiences, impacts, and outcomes of tele-retina screening for diabetic retinopathy among women in low socioeconomic groups.

Social Determinants of Health

Social determinants of health are conceptualized in a manner that takes into account how environmental and material conditions further increase the risk for marginalized populations at the intersection of identities such as race, age, gender, and income [22-24]. Social determinants of health in the context of mobile health screening among marginalized populations take into consideration environmental stressors that an individual may be exposed to, including but not limited to toxins, dwelling living conditions, access to education, food, employment, the role of a globalized economy and its effects, and current social exclusionary measures exacerbated through limited access to basic needs [22-24].

Integrating a socioeconomic approach provides an integrative synergistic framework in further understanding the material effects and experiences of diabetic retinopathy screening among women with low SES. Embedded within the framework is a social, economic, and political system approach for uncovering health inequities that are heavily influenced by these systems [23-25]. In this context, social determinants of health are elevated to include systems that perpetuate oppressions in relation to these material effects, such as poverty and inaccessibility to housing, food, and employment, which further compounds the overall health and well-being of women with low SES [23-26].

Health Equity

Health equity outcomes are directly correlated with the distribution of resources within any particular context. Women of low SES with multiple health conditions and limited access to resources have decreased access to achieving health equity. When deconstructing health equity, the construct of power relations within social, economic, and political systems is taken into consideration, as it determines the success rates for health- and well-being-specific interventions, including but not limited to promotion of health, interventions, and evaluation of the effectiveness of health-specific programs [22]. In considering the Social Determinants of Health framework, health equity, specifically the concept of power relations with a distribution of resources, is integral to understanding how successful health

promotion and intervention will be sustainable for marginalized populations [22]. Figure 1 illustrates the synergy of adapting the Social Determinants of Health framework with health equity

[22], and Figure 2 illustrates the Danaher framework (2011), which integrates the role of community in health policy advocacy for addressing health disparities [27].

Figure 1. Conceptual Social Determinants of Health framework (adapted from the World Health Organization).

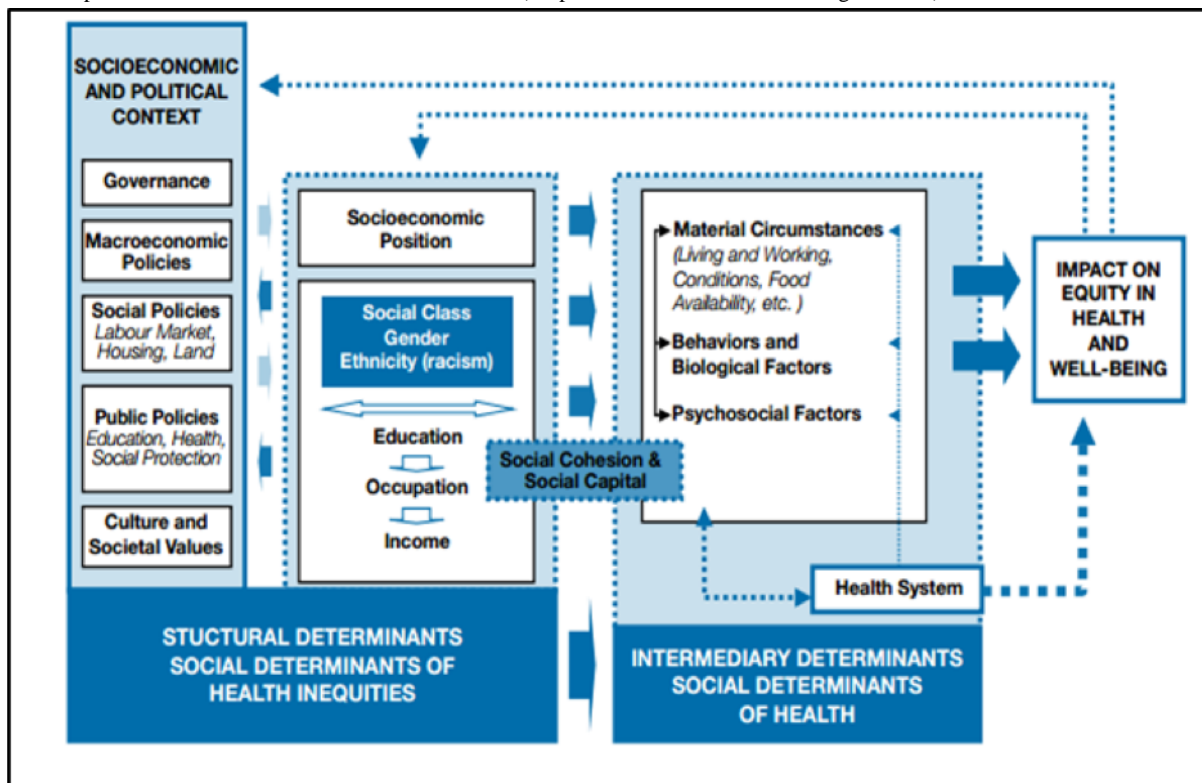
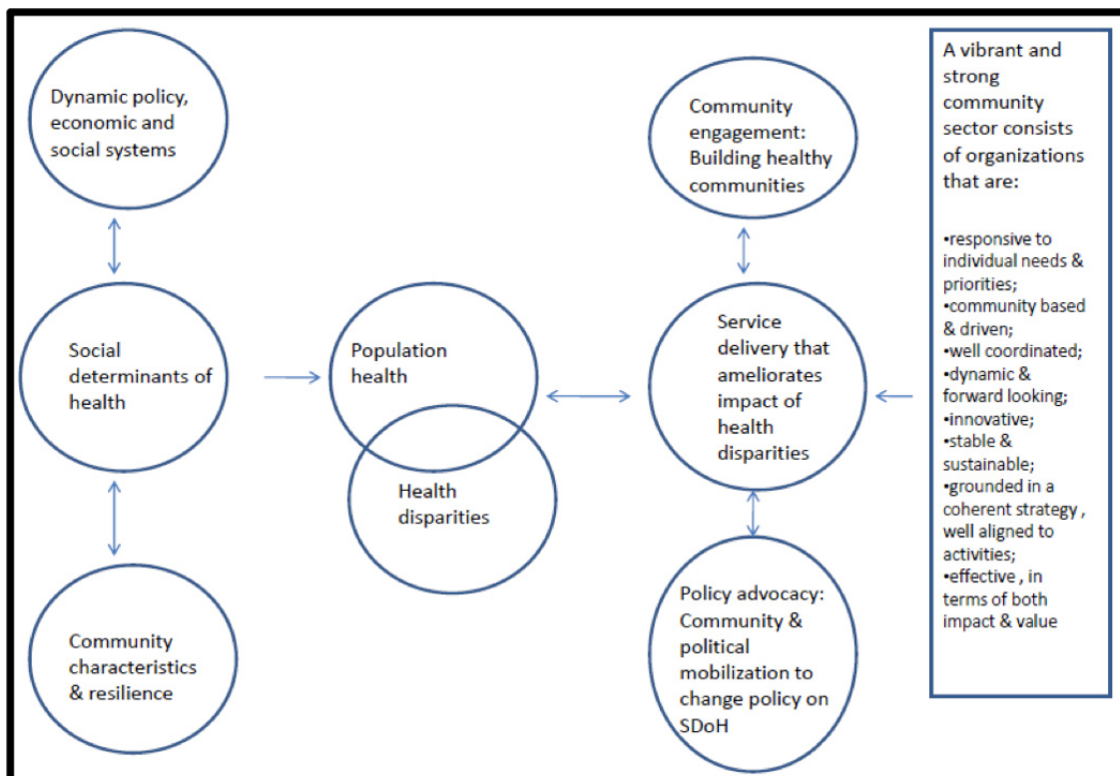


Figure 2. Danaher framework. SDoH: Social Determinants of Health.



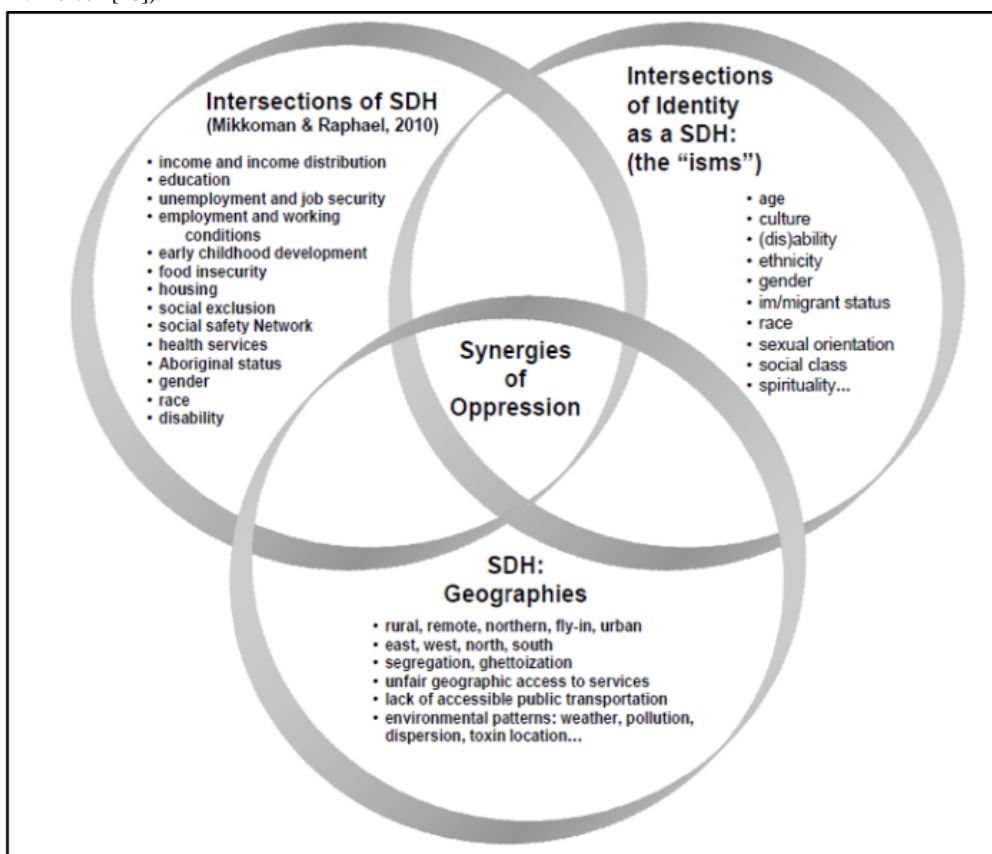
Intersectionality

Intersectionality is a theoretical and pragmatic tool within health service and system research to further nuance the complexities of the impact of health promotion and intervention among marginalized populations. Originally developed by Black feminist scholar Kimberle Crenshaw (1989), it has been adapted and interrogated to be applied in many other contexts within the sciences, social sciences, and humanities [23]. Marginality in relation to an intersectional approach takes into consideration that identity markers, such as age, race, gender, disability, and SES, are not viewed as separate and are rather interwoven with the outcomes involving how power relations within social, economic, and political systems further create health inequities through inaccessibility to resources for health promotion and intervention [23-26]. Intersectionality is taken up in this conceptual framing of an intersectional categorical axis where social determinants of health, systems of oppressions, and

environmental factors are integrated [23-26]. Figure 3 illustrates these categories/framings within the context of the synergy of oppressions, specifically the outcomes of increased marginalization through oppressions and intersections of social determinants of health. This synergy is also compounded with access to health equity [26,28].

For the purpose of this study, social determinants of health, health equity, and an intersectional approach to analysis are integral for understanding the impacts and material effects of diabetic retinopathy screening among women of low SES. This adapted framework provides an in-depth approach to understand how power relations within social, economic, and political systems impact community-based health screening programs for marginalized populations. Further, it integrates the individual standpoint based on intersectional identities and the environment.

Figure 3. Multiconstruct intersectionality framework (Synergies of Oppression) for addressing social determinants of health (SDH) inequities (adapted from McGibbon & McPherson [28]).



Program Description

In 2014, South Riverdale Community Health Centre (SRCHC), in partnership with Dr Michael H Brent, Chief of Retina Services at the University of Toronto, received funding from Toronto Central Local Health Integration Network to develop a mobile screening program to assess the retinal health of individuals diagnosed with diabetes (Figure 4) [29]. This strategy is driven by the recognition that access to optometrists and ophthalmologists is difficult for individuals with diabetes who live in certain neighborhoods in Toronto.

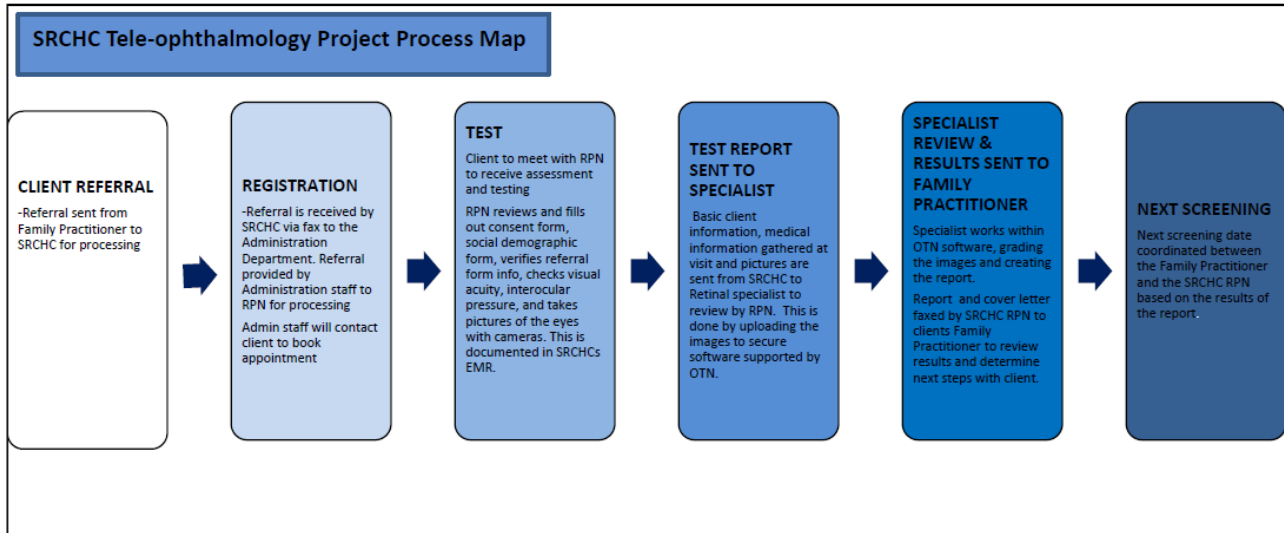
The tele-retina program is offered to patients at no cost in partnership with primary care organizations with a population focus (Anishnawbe Health Toronto) or in low-income communities with high prevalence of diabetes and low diabetic retinopathy screening rates (Parkdale, Flemingdon Park Community Health Centre, Scarborough Academic Family Health Team, LAMP Community Health Centre, Unison Health, Community Services-Lawrence Heights Site, and Unison Health and Community Services sublocations [Bathurst-Finch, Jane-Trethewey, and Keele-Rogers]) [29,30].

As of December 2016, the Toronto Health Economics and Technology Assessment Collaborative has created a very strong

collaboration with SRCHC where Toronto Health Economics and Technology Assessment assessed the cost-effectiveness of the screening program [31]. In 2019, findings from a cost-effectiveness study suggested that tele-retina is a more

cost-effective means of screening for diabetic retinopathy than the standard of care screening in urban and rural underscreened communities, and this study represents a natural progression of the previous collaborative work.

Figure 4. South Riverdale Community Health Centre (SRCHC) tele-retina project process map [30]. EMR: electronic medical records; OTN: Ontario Telemedicine Network; RPN: Registered Practical Nurse.



Methods

Guidelines

This protocol has been developed in accordance with SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [32].

Aims

We aim to explore the gender disparity in the provision of tele-retina program services for diabetic retinopathy screening in a cohort of women of low SES receiving services in SRCHC between 2014 and 2019, including but not limited to the evaluation of the overall patterns of tele-retina program use, and to conduct a qualitative study of patients, providers, administrators, and decision makers in order to understand their perceptions regarding the facilitators and barriers associated with the implementation and adoption of the tele-retina program.

Study Population

Quantitative Component

The population of interest includes individuals of low SES (income less than CAD \$25,000) attending diabetic retinopathy screening services at various sites (listed in Table 1) from 2014 to 2019, who have a diagnosis of diabetes, are at high risk for remaining unscreened for diabetic retinopathy, and have limited access to eye care.

SRCHC annually serves a population of 10,000 individuals, of which about 13% are diagnosed with diabetes and should undergo diabetic retinopathy screening. Annually, close to 500 individuals diagnosed with diabetes and receiving services from SRCHC are screened for diabetic retinopathy. As the program has been in place since 2014, we anticipate the study cohort will consist of 2500 individuals (500 individuals screened for diabetic retinopathy per year × 5 years [from 2014 to 2019]).

Table 1. Breakdown of recruitment (qualitative component) based on participating sites.

Site	Number of patient interviews	Number of health care provider, administrator, and decision maker interviews	Number of hours of observation
Anishnawabe Health Toronto	2-3	1-2	1-2
Flemingdon Health Centre	2-3	1-2	1-2
LAMP Community Health Centre	2-3	1-2	1-2
Parkdale Community Health Centre	2-3	1-2	1-2
Scarborough Academic Family Health Team	2-3	1-2	1-2
South Riverdale Community Health Centre	2-3	1-2	1-2
Unison Health and Community Services	2-3	1-2	1-2

Qualitative Component

The population of interest includes those who identify as women of low SES who attend or decline to attend tele-retina screening for diabetic retinopathy within one of the identified sites. The study population also includes health care providers, administrators, and decision makers who are involved in the tele-retina screening program.

Within the qualitative component, in addition to interviewing providers, administrators, and decision makers, we will purposely select a subset of the population from the quantitative component, more specifically those identifying as women of low SES who attend or decline to attend tele-retina screening for diabetic retinopathy within one of the identified sites.

Inclusion Criteria

Patients who are aged 18 years or above; identify as women of low SES (income less than CAD \$25,000); are able and willing to provide verbal and/or written informed consent; and attend (complete or decline) tele-retina screening for diabetic retinopathy are considered for inclusion. Please note that there are no language requirements, as we will use a translation services for non-English speaking clients.

Health care providers who currently provide care and are part of the screening process within the tele-retina program are considered for inclusion.

Administrators who coordinate the tele-retina screening for diabetic retinopathy and decision makers who inform and/or are part of the decision-making process for tele-medicine-specific programming within community health centers in Ontario are considered for inclusion.

Exclusion Criteria

Patients who are aged less than 18 years; do not identify as women of low SES (income less than CAD \$25,000); and are unable or unwilling to provide verbal and/or written informed consent are excluded.

Health care providers who are not practicing health care providers in the tele-retina screening for diabetic retinopathy program and are unable or unwilling to provide verbal informed consent are excluded.

Administrators and/or decision makers who are unable or unwilling to provide verbal informed consent are excluded.

Data Collection

Quantitative Component

In the retrospective cohort study, we will collect data on the overall patterns of tele-retina program use, including descriptions of program utilization rates (such as data on received and completed diabetic retinopathy screening referrals) along the landscape of patient populations receiving these services.

Qualitative Component

The qualitative component will entail collection of primary data sources to ensure rigor and data quality, including (1) nonparticipatory observations (ethnographic observations), (2) semistructured interviews, and (3) document review.

We anticipate a total of 7 to 14 hours of nonparticipatory observations (1-2 hours of observation per site) to observe how providers carry out their work on a daily basis, how administrators interact with providers, how patients and providers interact, and how patients interact with their environments. Field work provides excellent opportunities to identify and engage respondents for interviews and to collect grey literature. For all such field work, we will document activities, impressions, and interactions through field notes. Interviews lasting approximately 60 minutes will be guided by open-ended semistructured interview guides, and recorded and transcribed verbatim [33]. Interview guides will ensure that interactions among the researcher and participants remain focused and will be modified as new themes or issues arise, in line with the qualitative approach [34]. [Textbox 1](#) provides a detailed description of ethnographic field work and semistructured interviews.

We will collect and review relevant documentary sources on the operation of the tele-retina program, as processes within organizations are frequently text based and may serve as a substitute for records of activity [35]. Documents (eg, scientific papers, conference reports, organizational histories, press releases, and news stories) may provide access to an accepted body of knowledge about the role, policy, and procedures of an organization [36]. Documents will be collected by searching for publicly available documents (eg, through organizational websites, citations, and database searches).

Textbox 1. Description of ethnographic field work and semistructured interviews per identified site.

<p>Ethnographic fieldwork</p> <ul style="list-style-type: none"> • Process and interaction between the patient and health care provider during the tele-retina screening process for diabetic retinopathy (7-14 hours in total) <p>Semistructured interviews per identified site</p> <p><i>Patients</i></p> <ul style="list-style-type: none"> • 2-3 one-on-one semistructured interviews per site • Patients who identify as women of low socioeconomic status • Impact, experience, and outcomes of participating in the screening process <p><i>Health care providers</i></p> <ul style="list-style-type: none"> • 7-14 semistructured interviews • Nurses, physicians, and/or ophthalmologists involved in the screening process • Impact and experience of coordination, and delivery of the program <p><i>Administrators/decision makers</i></p> <ul style="list-style-type: none"> • Up to 14 semistructured interviews • Health care administrators/decision makers • Values and beliefs that inform the screening program • Description of the coordination, delivery, funding, and policies that inform the screening program
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Analysis

Quantitative Data Analysis

Continuous variables will be described using measures of central tendency and dispersion, such as mean/median and standard deviation/interquartile range, with appropriate statistical methods, and compared using analysis of variance (ANOVA) or the Kruskal-Wallis test as appropriate. Categorical variables will be described using contingency tables and compared using the chi-square test. Multivariate logistic regression will be utilized to assess the association between client characteristics, screening referral sources, and diabetic retinopathy screening. Analyses will be conducted using SAS v 9.4 (SAS Institute).

Qualitative Data Analysis

Data analysis will be an iterative and inductive process using a grounded theory approach [37]. This will involve systematic coding of data and theme abstraction to identify key facilitators and barriers to tele-retina intervention across the sites to ensure that our findings will inform recommendations appropriate to their context. Thematic analysis of the interview transcripts, interview notes, and observation notes will occur in the following three stages: open coding (data reduction), axial coding (data display), and selective coding (conclusion drawing). Comparisons within and across the interview data will be conducted (constant comparison technique) [38]. Multiple readings will be used, and alternative explanations of the data will be explored [39,40] to develop the most plausible and robust interpretation of the findings in order to obtain a comprehensive understanding of the facilitators and barriers to diabetic retinopathy screening [41,42]. All final themes will be informed by continuous dialogue among the research team. This dialogue

will facilitate self-reflection on how the analysis evolved to allow the qualitative lead to fully interrogate potential assumptions or biases reflected in the interpretation of the data [37]. Reliability of the findings will be strengthened by maintaining a chain of evidence throughout the study to ensure that the evolution of qualitative results can be followed by an external observer in order to ensure credibility of the data collection and analytical process. Data will be stored and managed electronically using the qualitative research software NVivo 11 (QSR International).

Convergent Analysis and Interpretation

We will utilize a convergent mixed methods design, which will combine and contrast the data collected in the quantitative and qualitative components in order to triangulate similarities and differences in the results of both research methods [43]. The findings will summarize and interpret to what extent the results from the two components converge, diverge, and produce a more complete understanding of the use of tele-retina services among women of low SES receiving care at SRCHC [43].

Results

For the quantitative study, we anticipate a cohort of 2500 patients, which will provide descriptive information on patterns of use of the tele-retina program. In total, we plan to interview 14 to 21 patients and 7 to 14 providers, administrators, and decision makers, and to conduct 7 to 14 hours of observations in order to gain an understanding of the facilitators and barriers to diabetic retinopathy screening. Please note that the interview guide is being developed in collaboration with our patient partners. The study is under review by the University Health Network Research Ethics Board (19-5628). We responded to

the first set of Research Ethics Board comments and are anticipating Research Ethics Board response. We expect to begin recruitment in winter 2021, as the tele-retina program has recently resumed at SRCHC.

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Discussion

This protocol outlines a study designed to understand the critical facilitators and barriers of the delivery of diabetic retinopathy screening among vulnerable communities. With the increasing incidence and prevalence of diabetes worldwide, morbidity, mortality, and associated costs due to diabetes-related complications remain a growing public health concern [44]. Diabetic retinopathy represents a global epidemic, as 191 million individuals worldwide will be diagnosed by 2030 [44], and the disease burden remains concentrated among low-income groups [45,46]. Emerging evidence illustrates that often interventions

aim to improve access to care, but may not be well adapted to vulnerable populations [47]. Understanding the facilitators and barriers of screening in this population will address the knowledge gap and assist in developing, implementing, and adopting effective, yet culturally sensitive, diabetic retinopathy screening interventions and thus carries promise in reducing the burden of blindness resulting from diabetic retinopathy. The findings should generate a deeper understanding of the ways in which system-level organizational interventions may improve access to screening for vulnerable populations and new knowledge with regard to improvements in the delivery of diabetic retinopathy screening interventions. Considering the widespread burden of diabetic retinopathy across the globe, the findings will be disseminated to ensure that strategies for the prevention and treatment of diabetic retinopathy are sensitive to vulnerable populations and can be implemented and adopted at the global level.

Considering that previous work has found tele-retina screening to be a more cost-effective alternative to standard care and that there is an increasing global burden of diabetic retinopathy, there is a need for improved access to care for vulnerable populations. National and international scaling and adoption of the tele-retina program to assist vulnerable populations may contribute to system-level cost saving.

Conflicts of Interest

None declared.

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Abbreviations

- CNIB:** Canadian National Institute for the Blind
SES: socioeconomic status
SRCHC: South Riverdale Community Health Centre

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Protocol

Development of a Web-Based Intervention Course to Promote Students' Well-Being and Studying in Universities: Protocol for an Experimental Study Design

Henna Asikainen^{1*}, PhD; Nina Katajavuori^{1*}, PhD

Faculty of Educational Sciences, University of Helsinki, Helsinki, Finland

*all authors contributed equally

Corresponding Author:

Henna Asikainen, PhD

Faculty of Educational Sciences

University of Helsinki

Viihkaari 9, PO Box 59

Helsinki, 00014

Finland

Phone: 358 445532494

Email: henna.asikainen@helsinki.fi

Abstract

Background: The decline in the well-being among university students well as increasing dropouts has become a serious issue in universities around the world. Thus, effective ways to support students' well-being and their ability to study are highly needed.

Objective: The purpose of this study was to build an intervention course for university students, which promotes both students' well-being as well as their learning and study skills, and to describe the experimental study design that explores the effects of this intervention course.

Methods: Research has shown that psychological flexibility has a great effect on the well-being as well as the study skills of students pursuing higher education. The basis of our intervention course was to promote psychological flexibility and students' study skills with the help of peer support and reflection.

Results: This course was offered as a voluntary course to all the students at the University of Helsinki twice during the academic year 2020-2021. The first course was from October to December and the second course was from January to March. This course was advertised in fall 2020 through social media and by different student organizations and program leaders at different faculties of the University of Helsinki. As of October 2020, we enrolled 566 students comprising 310 students for the course in fall 2020 and 256 students for the course in spring 2021. Of the 256 students who enrolled in the second course, 170 students voluntarily participated in this study and they answered the questionnaires, including all the measures, simultaneously with the participants in the first group and thus served as the control group. The effect of this course will be measured with multiple data, including questionnaire data, reflective journals, and physiological data of well-being with a longitudinal experimental design. This research very strictly follows the ethical guidelines drawn up by the Finnish National Board on Research Integrity. We expect to publish the results of this study in fall 2021 at the latest.

Conclusions: We argue that a web-based, 8-week intervention course, which promotes both student well-being and their study skills, is a good way to support students pursuing higher education, and both aspects should be considered when supporting university students.

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KEYWORDS

approaches to learning; psychological flexibility; well-being; online intervention tool; peer support; reflection

Introduction

Brief Overview of This Study

The decline in the well-being of university students and increased mental disorders experienced by students pursuing higher education have become a serious issue around the world [1-3]. In the United States, over 50% of the college students have a psychiatric disorder and over 60% have experienced serious anxiety [4]. In Finland, one-third of the students have experienced mental problems [5]. At the same time, there has been an increase in student dropout rates and study times have increased. As in most European countries, in Finland, 3 important aims to solve this problem have been added to the agenda: students' completion of degrees, completion in a reasonable period, and reducing student dropout [6]. In addition, the demands of today's workforce life require excellent life-long learning skills in students and the ability to solve complex and multidisciplinary problems under heavy workloads and stress. Thus, there is a huge discrepancy between the demands set for students and students' well-being. Obviously, there is a need for services that would enhance students' well-being, especially in the initial stages of studying due to the transition challenges being faced [7]. A growing body of evidence demonstrates that social and emotional skills greatly affect academic performance [8] and students' studying and learning are related to their well-being [9]. Furthermore, there is evidence that many students encounter troubles in their learning and studying processes [10,11], and in higher education, the emphasis should also be paid to supporting students by considering both their well-being as well as their study skills and life-long learning skills [12]. Thus, effective ways to support students' well-being and their ability to study are highly needed. Our aim was to describe a course that was developed to support students' well-being as well as their study skills at university and to describe the plan for how to explore the effects of this course on students' learning and well-being. This course was based on fostering students' psychological flexibility and study skills, and peer support and reflection were chosen as the central pedagogical tools to support the development of these aspects.

Theoretical Background

Well-being is not easy to define because there are many definitions and traditions and things to consider when thinking about well-being [13]. One prominent model of well-being defines well-being as having the following 3 parts [14]: emotional, psychological, and social well-being. Emotional well-being can be described as positive emotions toward life or good satisfaction in life. Psychological well-being relates to how individuals view themselves as functioning in life and it can be conceptualized through processes such as self-acceptance, sense of mastery and competence, positive relationships with others, feeling of personal growth or development, sense of goal-directedness in life, and autonomy [15]. Social well-being also refers to positive functioning but from a social perspective and it can be understood from 5 dimensions: social coherence, social acceptance, social actualization, social contribution, and social integration [16]. In this course, we aim to promote all 3 aspects of well-being, namely, emotional, psychological, and

social well-being by practicing and developing one's psychological flexibility.

Psychological flexibility describes people's ability to be connected with the present and to regulate their emotions and actions despite the unpleasant feelings or thoughts they might have [17-19] and further, to take value-based actions. People with high psychological flexibility act according to their own values and accept their negative thoughts, emotions, and sensations rather than avoid them and deal with these negative emotions and thoughts by opening up to them and observing them from another perspective mindfully [20]. The origin of psychological flexibility lies in acceptance and commitment therapy (ACT) [17,18] and is based on the ACT theory of psychopathology. Promoting psychological flexibility has been shown to improve all aspects of well-being: emotional, psychological, and social well-being [18,21]. It is related also to physical well-being as it is negatively related to experiences of, for example, sleeping problems [22] and eating disorders [23]. Research and meta-analyses have shown that psychological flexibility can reduce depression and anxiety [24,25] and has been found to play a central role in stress management [26] and life management [27], low quality of life, stress management and well-being [28,29], as well as self-compassion [30]. It has also been shown to have a central role in improving performance, well-being, and results in the workplace [31,32]. Some ACT-based interventions have been made in higher education and they have shown to be successful in improving students' well-being and stress levels [21,32-35] as well as their psychological flexibility [21]. Furthermore, ACT-based web-based interventions have been found beneficial in a meta-analysis of comparison between face-to-face and web-based interventions as there were no differences in the effectiveness, and thus, strong support has been brought up for the adoption of web-based psychological interventions [36].

Psychological flexibility is established through 6 overlapping core processes, which are strengthened in ACT. These core processes are acceptance, cognitive defusion, being present, self as context, values, and committed action [18]. Acceptance is the opposite of experiential avoidance and means "the active embrace of those private events occasioned by one's history without unnecessary attempts to change their frequency of form" [18]. Acceptance is not a matter of tolerance but rather, it supports value-based actions and exploration of feelings, memories, and thoughts from an observer perspective [37]. Cognitive defusion represents the process or techniques through which one's relationship to these negative thoughts is altered and the ability to look at one's own thoughts as separate parts of internal behavior and not consider them to be truth about the world or oneself [38]. Being present relates to continuous contact with a range of events or thoughts as they occur, emphasizing the ongoing process of defused and nonjudgmental description of thoughts [18]. Being present comprises seeing oneself as a context or a container of one's experiences and thoughts, and thus, seeing these thoughts as being separate from the self [17]. Values are the foundation for fostering psychological flexibility, and value-based action and behavior are necessary to life satisfaction and experience of a meaningful life [36,39]. Values are also an important part of psychological

flexibility as they offer guidance in terms of what behaviors are likely to lead to long-term satisfaction and experience of meaningfulness in life, which is an explicit aim in ACT [18]. The sixth aspect of flexibility, that is, committed action, leads to a value-emphasized life through taking value-based actions, instead of actions motivated by avoidance of negative thoughts [18]. Psychological flexibility has also a big role in university studies. It has been shown to be positively related to positive emotions in learning [40], integration into studying [41], self-regulation [42,43], and study progression [39,40]. Recent pilot studies have indicated that the theory of psychological flexibility is the core process in explaining procrastination in the higher education context [43,44] and it has also been shown to be particularly important for students who are at higher risk of academic failure [45]. Thus, the importance of psychological flexibility is evident in the university context. For this reason, all its 6 processes will be promoted and practiced in our course in order to foster the development of psychological flexibility.

In addition to psychological flexibility, research has shown that the deep approach to learning, that is, deep level processing in meaningful learning, is related to better learning outcomes [46,47]. However, recent research has pointed out that the deep approach to learning is not enough if the students are not organized in their studying [11,48]. Thus, the role of organized studying in significant in successful studying at a university [49-51]. Organized studying includes good time-management and self-regulation skills. Research has shown that it is possible to promote students' time-management skills through interventions in which students learn and practice organizational skills [52,53]. Furthermore, research has shown that students' approaches to learning are related to students' well-being at the university, thereby showing that poor study skills can lead to a risk of study-related burnout in studies [9] and further, time allocation to important activities is a central part in achieving a meaningful life [54]. For these reasons, it would be important to support students' time-management skills in order to improve their studying as well as to help students to allocate time better to things that are important to them. As deep approach to learning is related to better achievement as well as better well-being, it is utmost important to enhance both students' time-management skills as well as their deep-level learning.

In summary, both psychological flexibility and study skills, including good time-management skills, are needed to foster university students' well-being and studying. Thus, our intervention course is based on practicing both these aspects. Two central tools to foster these aspects during the course are reflection and peer support. Reflection has a central role during this course because reflection supports learning, and deeper and critical reflection is related to deeper learning, and further, to better learning outcomes [55]. In addition, research has shown that peer support is related to successful study progression and it is a central factor to enhancing studying at the university [51].

Peer support has also been found to be important in increasing well-being [56].

Our aim was to develop a course to support students in being successful in their studies by supporting different aspects of well-being (physical, emotional, social, and psychological) as well as their study skills and further, to study the effects of this course. The central process to support these aims is to support the development of psychological flexibility as it has been shown to have positive effects on all aspects of well-being as well as learning and studying in higher education. We will now describe the course in more detail and the experimental study design with a control group for studying the course.

Methods

Intervention Course


An optional 8-week ACT-based web-based course was developed on the Moodle web-based platform and was completed online. This course was designed so that students do weekly assignments independently, reflect the themes of the course in small groups, and give and receive peer feedback of each other's assignments. The course is suitable for Bachelor and Master level students and can be easily implemented to curricula. The teacher's role in this course is to facilitate students' progress during the course and monitor the group discussions and students' assignments. The teachers also meet the students online in the course and give video instructions to the module's themes and assignments. The teachers need to be familiar with the process of psychological flexibility as well as study skills to guide students properly and thus, training has been given to the teachers.

Modules of the Intervention Course

This intervention course consists of 8 modules, each module lasting for 1 week (Figure 1). The course was developed to last for 1 study period. In the University of Helsinki, there are 4 study periods in 1 academic year, each period lasting for 8 weeks. Modules support the development of psychological flexibility and study skills. Each module focuses on to 1 or 2 processes of psychological flexibility. The processes are parallel to each other [17] but some processes are emphasized more in some of the modules. Each module includes video and text introductions to the themes of the week—individual experimental and reflective assignments—in which participants are asked to write down their experiences and reflections. In addition, small group discussions about the themes are held every week. We have developed introduction videos and materials for every week and part of the exercises and the assignments ourselves, but the exercises targeted to improve psychological flexibility are based on the work that has been done by Hayes [18] and a Finnish ACT psychologist Arto Pietikäinen who has also helped developing the course. Next, we present these modules in more detail.

Figure 1. The design of the course.

Introduction Module	Module 1	Module 2	Module 3	Module 4	Module 5	Module 6	Module 7
Evaluation of well-being and studying	THEME What is important: Subprocess: values	THEME Focusing on the present: Subprocess: Being present/acceptance	THEME Power of thoughts Subprocess: Cognitive defusion/self as context	THEME Coping with studying: Subprocess: committed action	THEME Acceptance and self-compassion: Subprocesses: acceptance, self as context	THEME Value-based action: Subprocess: committed action Learning report	individual feedback from peers
Introduction to the course and themes							
Start of peer group work	Group discussion and reflection	Group discussion and reflection	Group discussion and reflection	Group reflection assignment	Group discussion and feedback	Group discussion and reflection	

REFLECTION 

Introduction Module

The Introduction module includes video introductions to the course and an introduction to the central theme of the course: psychological flexibility and well-being. This module includes all the practical information about course assignments and completing the course, including deadlines and guidelines for group work and giving peer feedback. To help students reflect on their well-being and studying, students evaluate their level of well-being and study skills with validated research instruments at the beginning of the course and receive web-based feedback on these evaluations. For example, students receive feedback about their risk of study-related burnout and receive feedback and guidance according to the results they receive. The same evaluations are also completed at the end of the course. The aim of the evaluations is to stop students to consider their well-being in more detail right at the beginning of the course, and further, to help them reflect the change in their evaluations during the course. Students are also offered to do simple exercises on promoting psychological flexibility and they start a time-management assignment in which they are asked to monitor and record their time usage for a week. The aim of this task is to help students become aware of their time usage and help them in the forthcoming assignments during this course. The time-management task is used to help students to develop their studying by helping them to improve their time-management skills, setting goals, and to allocate time to important things in life. In addition, the students also start the group work by introducing themselves to the peer group and sharing thoughts about the start of the course.

First Module

The theme of the *first module* is *What is important*. This module consists of materials and exercises related to one’s values. First, introductions to values and why they are important to consider are represented. In addition, students do exercises that help them to think about and clarify issues that are important to them in their life. For example, students are asked to think about themselves far into the future having lived a very good life and are asked to think about the things they could remember about their lives and what they valued. In addition, students are asked

to think about several areas of life such as well-being, family, friends, and to think about what is important for them and what they could do to foster this value. After these exercises, students set a value-based goal that they would want to achieve, and this goal is revisited and monitored throughout the course. To help the students reflect on how their values are manifested in their lives, students have a group discussion where they reflect their thoughts about the time-management task and how time management could help with the achievement of the goal.

Second Module

The theme of the *second module* is *Focusing on the present*. This module focuses on practicing 2 subprocesses: being present and acceptance. In this module, introductions are given to what being present really means, how it affects our brain and learning, and why it is important. The exercises include mindfulness exercises, which also include practice of acceptance of bodily emotions and thoughts. In the exercises, students are, for example, asked to do something mindfully by paying attention to this situation (waiting for a bus, eating, etc) or students are instructed to be intentionally present and listening when communicating with a peer. This module also includes breathing and relaxation exercises. Students are asked to test these different kinds of exercises during the day and monitor how these exercises affect their well-being. A small group discussion is also included where students are asked to share their experiences of the exercises and how these exercises have affected their studying and well-being and could help them achieve their goals.

Third Module

The *third module* is related to the theme *Power of the thoughts*. This is related to 2 of the central processes of psychological flexibility, namely, cognitive defusion and self as context. First, introductions are given to thoughts, how powerful they are, how they are related to emotions, and why it is important to become conscious of one’s thoughts. With different exercises, students are encouraged to become conscious of their thoughts, to explore and test these thoughts, and to look at their thoughts just as thoughts and not facts or truths about themselves or the current situations. For example, students are instructed to think about

their negative thoughts just as thoughts that are like floating leaves on a flowing river: they can be observed and they come and go. In addition, students are asked to find new alternative thoughts and think of the long-term effects of these different thoughts to their behavior and well-being. These exercises aim to help the students to change their relationship with the negative thoughts they might have. Students share their experiences and discoveries in small groups and further, they are asked to think of how becoming aware and accepting their thoughts can help them achieve their goals regarding studying and well-being. During this week, students also meet the teachers of the course online. The aim of this meeting is to discuss about the themes and questions of the course together with students and practice together to recognize some negative thoughts students might have related to situations in studying.

Fourth Module

The *fourth module* consists of exercises that are comprehensively related to the theme *Coping with studying*. This module focuses more on the studying ability, including study processes, general well-being, and on values and committed actions. This module consists of introductions to this theme, web-based lectures and assignments regarding studying ability, time management, and studying techniques. The significance of physical exercise, sleep, and nutrition in studying is also discussed to make studying and learning more effective. During this module, students are encouraged to think of their life habits (including sleeping, exercise, and nutrition) in order to reinforce the value-based actions related to these themes by testing and monitoring the effects of different exercises. Students are also asked to identify the issues and elements that contradict the student's own values related to studying or general life habits. Students practice study techniques, which support deeper understanding in their studying. Students are encouraged to apply these techniques to their learning and studying and to monitor which techniques and which practices would work best for them. During this week, students discuss in their peer groups about their experiences about that week's topics.

Fifth Module

The *fifth module* is related to the theme *Acceptance and self-compassion*, concentrating on subprocesses of acceptance and self as context. In this module, students continue with exercises and techniques, which help them to accept, confront, explore their thoughts, and concentrate on self-compassion exercises. Students are, for example, asked to monitor how they speak to themselves, what kind of thoughts they have toward themselves, and to practice compassion toward themselves. Students are asked to have a thankful attitude toward their lives and practice compassion toward their peers, for example, they are encouraged to do small actions such as calling a relative, which support their own values. In addition, they are asked to observe how this kind of behavior affects their well-being and studying. These exercises present common humanity of self-compassion. Finally, students are asked to reflect on these exercises in their peer groups and to think how these exercises affect their well-being and studying.

Sixth Module

The *sixth module* is related to the subprocess of *Committed actions*. This module consists of introduction to this theme and web-based lectures about the significance of committed value-based actions. Students are encouraged to become conscious of obstacles that hinder them to doing what is important to them and further, they practice engaging in actions that help them to achieve their goals, which are set up in the beginning of the course. Students write a final learning journal, in which they reflect on their learnings and experiences of the effects of the course on their studying and well-being, and further, they analyze how they have proceeded with the goal that they have set up in the beginning of the course. Furthermore, students evaluate their well-being and studying based on the questionnaires again and are encouraged to analyze the changes in their well-being and studying during the course. At the end of the week, students discuss in their peer groups about their experiences and ideas of how to enhance taking value-based committed actions.

Seventh Module

The *seventh module* is a *Concluding module*. Students provide individual constructive feedback of the reflective journals to 2 other students anonymously, and students have a final peer group discussion where they share their experiences of the course, including which exercises have been the most effective to them and why.

Results

The effect of this course will be measured with multiple data, and informed consent will be collected in the beginning of the course. First, questionnaire data measuring psychological flexibility [57], stress [58], social, psychological, and emotional well-being [59], study-related burnout [60], and study skills [61] will be collected before, after, and 1 year after the course. These questionnaires are also the basis of students' own evaluations in the beginning and at the end of the course. Students also receive feedback from these evaluations. Hierarchical linear modeling with full information maximum likelihood estimation will be used to examine changes over time. In order to test the impact of the self-assessment from premeasurement to postmeasurement, the Group×Time interaction will be explored. Second, qualitative data of the effects of the course will be analyzed comprising students' reflective journals of the course and open-ended responses about their experiences of the course in the questionnaire, which are used at the end of the course. These experiences will be analyzed for the effects of the course by using inductive content analysis [62]. In addition to self-reported data, physiological data of well-being will be used to measure changes in their well-being. The Moodmetrics smart ring, which measures electrodermal activity or level of arousal [63], will be used to measure participants' stress levels and how this stress level changes during the course compared to that in the control group. Recent research has found that Moodmetrics has been found to be a robust measurement of the stressfulness in the workplace [64]. Students will keep the ring on during the whole course, and changes in stress levels will be analyzed and compared between

the control and experimental groups by using methods of longitudinal analysis. Furthermore, we will also combine self-reported and biophysical data to compare the effects of the intervention from different data.

This course was offered as a voluntary course to all the students at the University of Helsinki twice during the academic year 2020-2021. The first course was from October to December and the second course was from January to March. This course was advertised in fall 2020 through social media and by different student organizations and program leaders at different faculties of the University of Helsinki. As of October 2020, we enrolled 566 students comprising 310 students for the course in fall 2020 and 256 students for the course in spring 2021. Of the 256 students who enrolled in the second course, 170 students voluntarily participated in this study and they answered the questionnaires, including all the measures, simultaneously with the participants in the first group and thus served as the control group. This research very strictly follows the ethical guidelines drawn up by the Finnish National Board on Research Integrity [65]. We expect to publish the results of this study in fall 2021 at the latest.

Discussion

Our aim was to develop a pedagogically reasonable and beneficial web-based course to support students' well-being as well as their study skills at university. We designed this intervention course to equip students with tools to enhance their

well-being and to help them develop their study skills because well-being should also be taken into account when fostering students' learning and studying [9,45]. This course was based on the idea of fostering psychological flexibility, which has convincingly been shown to be an essential factor in improving psychological, social, and emotional as well as physical well-being in many ways [25,35,66,67]. We will analyze the effects of this course with multiple data comprising quantitative, qualitative, and biophysical data in order to obtain comprehensive data of the effects.

During this course, each subprocess of psychological flexibility is systematically trained during the modules. Study processes and study skills are trained especially during 2 modules; however, studying is reflected throughout the course. We have implemented effective pedagogical tools to foster students' learning during this course, namely, reflection and peer group working. Thus, we expect to see positive effects on students' well-being and study processes during this course. A very small pilot study comprising similar elements showed that this kind of course can have many positive effects on students' well-being and study skills [68]. That pilot study was analyzed with only 20 students and had no control group, but open-ended experiences of the students indicated that the students had a positive attitude toward the course and that the course had a positive effect on their well-being and study skills [68]. We expect to obtain the preliminary data of this course in spring 2021.

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Conflicts of Interest

None declared.

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Abbreviations

ACT: acceptance and commitment therapy

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Protocol

Rapid Design and Delivery of an Experience-Based Co-designed Mobile App to Support the Mental Health Needs of Health Care Workers Affected by the COVID-19 Pandemic: Impact Evaluation Protocol

Matthew Lewis¹, BAPSC, PhD; Victoria J Palmer^{1,2}, BA, PhD; Aneta Kotevski³, BMEDSC, PhD; Konstancja Densley¹, MSc; Meaghan L O'Donnell⁴, BSc, MPsych, PhD; Caroline Johnson¹, MBBS, FRACGP, GCUT, PhD; Franz Wohlgezogen⁵, PhD; Kathleen Gray², MLS, MEnvSci, PhD; Kate Robins-Browne¹, MBBS, FRACGP, PhD; Luke Burchill^{6,7}, MBBS, PhD

¹Integrated Mental Health Research Program, Department of General Practice, Melbourne Medical School, The University of Melbourne, Melbourne, Australia

²Centre for Digital Transformation of Health, The University of Melbourne, Melbourne, Australia

³Department of Medicine, The University of Melbourne, Melbourne, Australia

⁴Phoenix Australia, Department of Psychiatry, The University of Melbourne, Melbourne, Australia

⁵Centre for Workplace Leadership, Faculty of Business and Economics, The University of Melbourne, Melbourne, Australia

⁶Department of Medicine, The University of Melbourne, Parkville, Australia

⁷Department of Cardiology, Royal Melbourne Hospital, Parkville, Australia

Corresponding Author:

Luke Burchill, MBBS, PhD

Department of Medicine

The University of Melbourne

Royal Melbourne Hospital

4th Floor, Clinical Sciences Building

Parkville, 3050

Australia

Phone: 61 3 8344 7161

Email: blj@unimelb.edu.au

Abstract

Background: The COVID-19 pandemic has highlighted the importance of health care workers' mental health and well-being for the successful function of the health care system. Few targeted digital tools exist to support the mental health of hospital-based health care workers, and none of them appear to have been led and co-designed by health care workers.

Objective: RMHive is being led and developed by health care workers using experience-based co-design (EBCD) processes as a mobile app to support the mental health challenges posed by the COVID-19 pandemic to health care workers. We present a protocol for the impact evaluation for the rapid design and delivery of the RMHive mobile app.

Methods: The impact evaluation will adopt a mixed methods design. Qualitative data from photo interviews undertaken with up to 30 health care workers and semistructured interviews conducted with up to 30 governance stakeholders will be integrated with qualitative and quantitative user analytics data and user-generated demographic and mental health data entered into the app. Analyses will address three evaluation questions related to engagement with the mobile app, implementation and integration of the app, and the impact of the app on individual mental health outcomes. The design and development will be described using the Mobile Health Evidence Reporting and Assessment guidelines. Implementation of the app will be evaluated using normalization process theory to analyze qualitative data from interviews combined with text and video analysis from the semistructured interviews. Mental health impacts will be assessed using the total score of the 4-item Patient Health Questionnaire (PHQ4) and subscale scores for the 2-item Patient Health Questionnaire for depression and the 2-item Generalized Anxiety Scale for anxiety. The PHQ4 will be completed at baseline and at 14 and 28 days.

Results: The anticipated average use period of the app is 30 days. The rapid design will occur over four months using EBCD to collect qualitative data and develop app content. The impact evaluation will monitor outcome data for up to 12 weeks following hospital-wide release of the minimal viable product release. The study received funding and ethics approvals in June 2020. Outcome data is expected to be available in March 2021, and the impact evaluation is expected to be published mid-2021.

Conclusions: The impact evaluation will examine the rapid design, development, and implementation of the RMHive app and its impact on mental health outcomes for health care workers. Findings from the impact evaluation will provide guidance for the integration of EBCD in rapid design and implementation processes. The evaluation will also inform future development and rollout of the app to support the mental health needs of hospital-based health care workers more widely.

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KEYWORDS

mental health; mobile applications; COVID-19; health personnel; experience-based co-design; impact; evaluation; digital interventions; app; intervention; health care worker; design; delivery; support

Introduction

Background

The mental health and well-being of health care workers should be a major public health priority [1] both during the COVID-19 pandemic and beyond to support the successful functioning of the health care system. Health care workers, particularly nurses and physicians, experience significant mental health challenges; these have been exacerbated during the early stages of the COVID-19 pandemic, with high rates of depression (23.2%), anxiety (22.8%), and insomnia (38.9%) reported [2]. Similarly high rates of clinically significant anxiety (45%), depression (38%), and posttraumatic stress disorder (19%) have been observed during and following significant viral outbreaks and pandemics [3]. Despite the recognized impact of pandemics on the mental health and well-being of health care workers, few digital solutions have been developed and delivered to support the mental health and well-being of hospital-based health care workers. A mobile app could provide readily available, evidence-based support for stress management, mental health, and well-being to hospital-based health care workers during the COVID-19 pandemic. By using experience-based co-design (EBCD) approaches, this app could deliver appropriate supports across professional groups.

Health care workers are often reluctant to seek appropriate and timely mental health support [4]. Perceived stigma and career impact, time challenges, and a work culture that values stoicism are recognized as contributing barriers to help-seeking [4-6]. Without support, all health care workers are at increased risk of major mental health complications [4,7]. Targeted approaches to maintain and improve the mental health of health care workers are needed that can address barriers to help-seeking and meet health care workers “where they are” according to their professional needs. A mobile app co-designed by health care workers offering mental health support may have potential as a readily accessible, cost-effective, evidence-based, and scalable tool to achieve these goals [8].

The more a mobile app integrates the lived experiences of health care workers through the use of co-design processes, the more likely it will be to respond to their needs and ideally lead to increased uptake and engagement. While digital health

interventions and mobile app development use human-centered design (HCD) principles to meet user needs [9], few embed and follow an EBCD approach. EBCD offers power sharing and approaches that can further extend HCD methods to develop deep insights that enable users to actively shape and co-design solutions [10]. EBCD has typically been used in health care quality improvement as a method for staff, patients, and carers to collaborate on the design of solutions drawing on narrative and story-based approaches through interviews, film, or other visual methods, such as digital stories, coupled with facilitated co-design using design thinking and participatory approaches. The integration of the lived experience of end users via EBCD processes will ensure that outcomes are targeted and co-designed with those most likely to be impacted by an issue, change to process, or intervention [11,12]. EBCD provides an avenue to more deeply embed end users’ experiences as the primary driver of change processes and provides a commitment to shared power arrangements and decision-making not currently addressed by the adoption of HCD principles alone [10]. The explicit use of EBCD as a way to embed lived experience will ideally result in greater uptake of the mobile app and increased engagement. Several digital mental health support responses for health care workers have been developed to address the impact of COVID-19 [13], and while some were led, peer-designed, and delivered by health care workers, we were unable to identify any that were co-designed by and for health care workers themselves. Addressing this gap may be part of what is required to improve overall uptake, engagement, and use of mobile apps by individuals. The RMHive app will attempt to do this by embedding health care workers in the design, development, and implementation of a mobile app using EBCD.

Integrating the lived experience of health care workers in the design and development of mobile apps is important to support their mental health needs [12]. Equally important is a systematic evaluation of the development process and outcomes that can be used to support replication of mobile apps or digital interventions. This includes outlining the underlying theoretical frameworks, clear overviews of the design, development, and implementation, and documentation of impact [8,14]. Existing evaluations focus on the development and implementation of mobile apps largely from a technological perspective; however, they can take a more limited evaluation of the wider contextual,

organizational, and individual factors that influence uptake and impact on outcomes [15]. A broader impact evaluation approach enables sociotechnical digital health perspectives to be considered in the context of intersecting factors and causal attributions across the design, development, and implementation continuum for programmatic scale-up [16].

This protocol describes the impact evaluation of the RMHive mobile app, which is being led by health care workers as an EBCD intervention for health care workers with mental health needs arising from the COVID-19 pandemic. Using EBCD, health care workers from different professional groupings will serve as co-design partners across all phases of research, from ideation to implementation. RMHive is not being developed as a clinical or therapeutic tool. The impact evaluation will integrate data from the design and development and the wider implementation of RMHive and lead to the formulation of a theory of change that can explain both positive and negative impacts to guide future delivery of the mobile app across other health services and hospital networks.

Objectives

A rapid design and development cycle will be adopted using EBCD to identify experiences and create an app prototype within 3-4 months to support the mental health needs of hospital-based health care workers working in the COVID-19 context. The adopted approach is analogous to rapid prototyping in design thinking [17] through the use of rapid co-design processes. The impact evaluation addresses three questions using quantitative and qualitative data that will be collected across all stages:

1. What is health care workers' engagement with RMHive, including use patterns, perceptions of content, and overall level of engagement?
2. What contextual, socio-technical, organizational, and individual features support or hinder implementation of the RMHive app?
3. What are the identifiable impacts on the mental health of individual health care workers through adoption, implementation, and use of the RMHive app?

This protocol will describe the planned design, development, and implementation of the RMHive mobile app using EBCD.

It will describe the data to be collected to inform the impact evaluation and the proposed analysis plan.

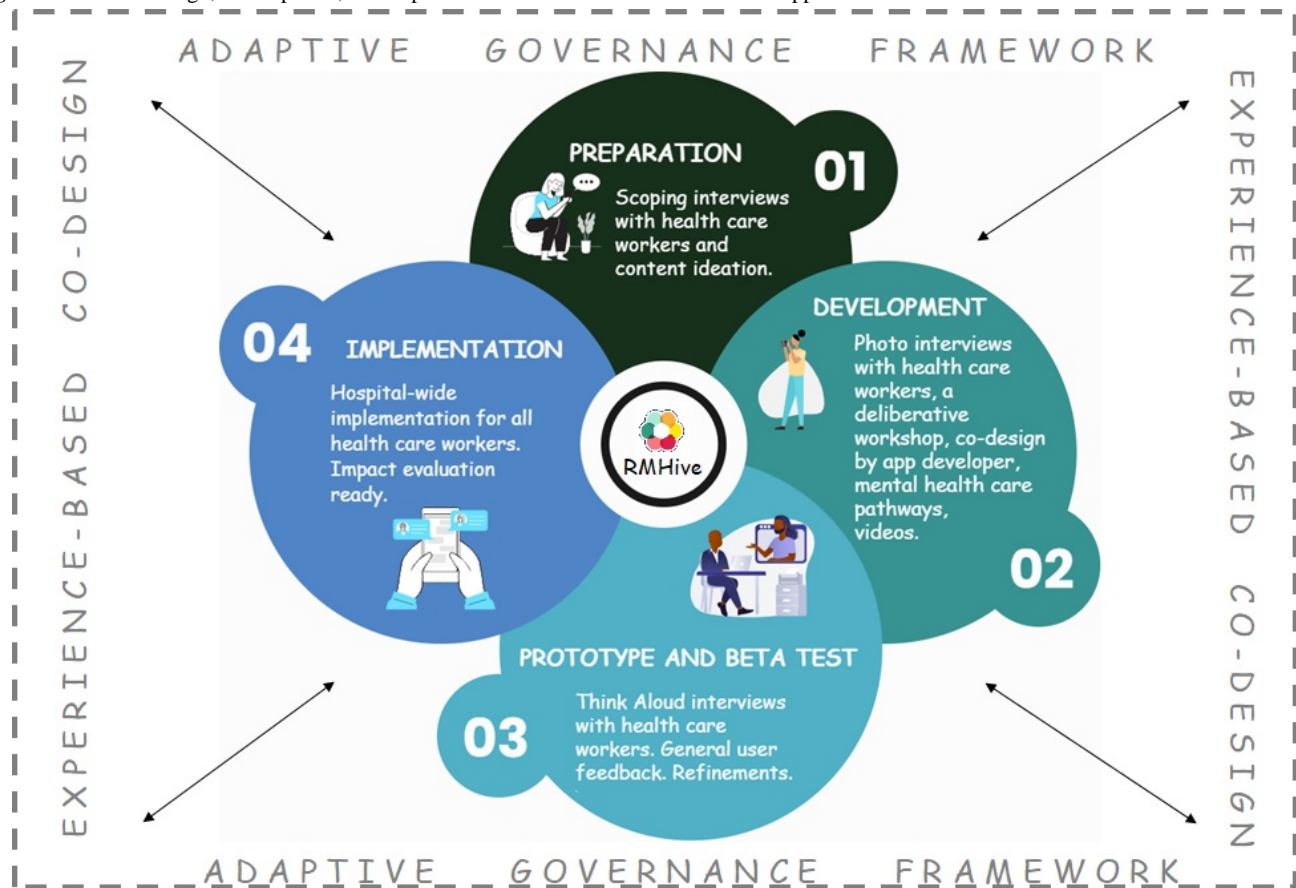
Methods

Setting and Locations

RMHive will undergo development, beta testing, and implementation with hospital-based health care workers across Royal Melbourne Hospital (RMH). RMH is a large tertiary referral hospital that includes two major campuses, an acute care city campus and a second inner city campus providing subacute services, including aged care; both campuses have been heavily impacted by the COVID-19 pandemic. RMH is the largest provider of mental health services in Victoria, with services spanning the northern and western suburbs of Melbourne. RMH is a part of the Melbourne Health Network, which reported 10,000 staff and volunteers in 2018/2019. In 2019, there were 79,799 presentations to the emergency department and 105,493 inpatient admissions [18]. Design, development, and beta testing will be conducted with the emergency and cardiology departments as two settings impacted by the COVID-19 pandemic. Following completion of the beta test phases and refinements arising from this process, RMHive will be implemented across RMH and made available to all health care workers hospital-wide. Although it is recognized that some context- and profession-specific needs may remain unaddressed in this preliminary rapid design process, a decision was made to perform a hospital-wide rollout of the app to explore use patterns and gather feedback to inform future iterations and refinements of the app. Ethics approval for this study has been provided by the University of Melbourne Human Research Ethics Committee (Ethics ID #2056866).

Overview of the RMHive Design, Development, and Implementation Process

The project will adopt a rapid design, development, and implementation process using EBCD to progress from needs identification of health care workers and content creation through to app design and development and beta testing to a minimally viable product (MVP) release. An overview of the design, development, and implementation framework is shown in [Figure 1](#).

Figure 1. Planned design, development, and implementation framework of the RMHive app.

Project and Governance Team

An important governance principle for the research team will be adaptiveness to ensure that the design and implementation process is sufficiently flexible to adjust to complex, unpredictable changes that may occur while undertaking the research (eg, due to emerging events throughout the COVID-19 pandemic). An adaptive governance framework will be adopted to support the design, development, and implementation of RMHive [19]. Adaptive governance provides a structured approach for decision-making in complex and dynamic systems while paying attention to the needs of grassroots community members [20]. Key to adaptive governance is shared decision-making arrangements that complement the collaborative and power-sharing goals of the EBCD approach. When applied to RMHive, adaptive governance is being used to ensure that health care workers from diverse professional backgrounds, including clinical workers (eg, nurses, physicians, psychologists, primary care specialists) and nonclinical workers (eg, administrative staff, environmental service assistants) are continually involved in shared decision-making and feedback across all phases of research and according to the changing community needs of health care workers. This extends to providing mechanisms of accountability of the research team in the EBCD processes.

The co-design and implementation of the RMHive app will be managed by a health care worker-led project team and will include health care workers in multiple project governance roles and as advisory committee members. Health care worker

members of the project team and advisors will be invited to participate through posters and flyers posted in staff common rooms and drawn from critical care emergency and cardiology units for the first rapid design phases. It is anticipated that the health care workers will most commonly be nurses and physicians, as these are the two largest professional groups in the hospital. The health care worker advisory group will provide input and feedback and share decision-making throughout the project. The adaptive governance framework supports feedback loops that ensure health care worker input is reviewed on a continuing basis, with decision-making shared by health care workers on the project team meeting every 2 weeks. The project team will be multidisciplinary and incorporate experts in EBCD, implementation science, evaluation, applied ethics, mental health clinical care, project governance, mental health care research and delivery, mobile app development, digital health interventions and evaluation, and creative content production.

Preparatory Phase

Prior to commencement of the co-design work, scoping interviews were conducted during the initial wave of COVID-19 in early 2020 with a small but diverse group of health care workers (N=6). These interviews were conducted to understand the experiences and needs of health care workers working during the pandemic. Semistructured interviews included scoping questions codeveloped by health care workers and the researchers leading the study (available upon request). The health care workers reported being overwhelmed with written communication (guidelines, clinical directives, news reports)

and expressed a clear preference for video- rather than text-based information. Using these experiences, the project team generated ideas for video-based content that reflected health care workers' experiences but that also responded to their needs. These were (1) mental preparation and coping strategies; (2) remaining connected through hearing other experiences of working on the front line; and (3) having a "time out"/a break from the "dark bubble" they were living in. The broad content themes were pitched to health care worker members of the implementation team and led to a decision to develop video content within the app.

Needs Analysis and Understanding Context

Leveraging the expertise of EBCD researchers working on the project team, health care workers selected photo interviews (photo elicitation) as a relevant method for understanding the mental health needs and lived experiences of health care workers. We have previously shown photo elicitation to be a relevant participatory visual method that can be successfully applied across different contexts and research settings [21]. Photo interview methods enable a narrative approach to identifying needs and understanding context [21] and can help people to articulate complex concepts, discuss sensitive topics, and provide insight into the inner worlds of feelings, emotions, and thoughts [22]. Up to 30 health care workers from the emergency and cardiology departments will be invited to participate in the photo interviews [21]. The choice of these departments was based on the professional groups representing the largest proportions of hospital staff.

The photo interview method will involve health care workers being asked to provide the research team with a series of 3-5 digital images produced on smartphones reflecting their experience of the COVID-19 pandemic, including challenges associated with working on the front line as well as experiences or behaviors that are helping them to meet these challenges. The images will inform a semistructured telephone interview to draw out key "touchpoints" related to the experiences of health care workers during the pandemic and the impacts on their mental health. A touchpoint is a term used in EBCD to refer to the places and the ways in which a person comes in touch with a particular service or organization, or how an issue touches them directly (eg, the subjective world of the person) [23]. The touchpoints will be further explored in a deliberative workshop to scope content areas to be developed within the app. The workshop discussion will be analyzed to identify one or two key touchpoints that will inform an additional co-design workshop to be conducted by the app developers, Curve Tomorrow (explained below).

Early in the RMHive development process, a series of interviews will be conducted with a diverse range of hospital managers and leaders within RMH (N=30) to gain insights into existing mental health programs, systems, organizational context, and services for the mental health of health care workers. It is likely that this group will be involved in initiatives for mental health, and this interview data will provide further contextual data to inform the implementation of RMHive and its impact evaluation.

Content Creation

Video content will be developed by a university-based video producer working with a team of externally based creatives, including filmmakers, animators, and script writers, based on the expressed needs and specific questions posed by health care workers in the preparatory phase, which resulted in the creative team receiving health care worker approval for four planned video series. The first series of videos will feature health experts answering questions posed by health care workers working on the front line during the COVID-19 pandemic. The second series will include animated videos developed in conjunction with Phoenix Australia, national experts in trauma-informed care, that focus on resilience and coping strategies (an issue that was raised by health care workers in the preparatory phase scoping interviews). Series 3 will include short videos based on themes identified by health care workers and that take a humorous tone based on feedback from health care workers that they needed a mental break from the daily challenges of the COVID-19 pandemic. The final series will be short films that use the audio taken from the photo interviews that address health care workers' need to connect with others, and the filmmakers will creatively reflect on their experiences. Health care workers identified the experience of discussing their work lives and challenges as cathartic, and the content creation team has engaged eight filmmakers who will be asked to respond to each audio interview with a short film in an attempt to maintain a creative dialogue between the health care workers and creative team. Closing the communication loop, the health care workers will then respond to the short film with a written reflection. The films and responses are both planned to appear in the app.

A team of mental health clinicians will develop information about clinical support pathways and curate existing digital and face-to-face mental health support services and tools to be included in the RMHive app. These resources will match the touchpoints identified in the photo interviews with health care workers. The goal is to provide targeted pathways for mental health support depending on the needs of users in a simple, private, and focused way in response to need. Engagement and feedback of health care workers in the preparatory phase scoping interviews of the study identified that options to self-monitor mental health would be valuable. This self-monitoring is intended as a reflective point for individuals and to provide personalized engagement opportunities in the app for the user.

The mental health team determined that the Kessler Psychological Distress Scale (K10) [24], a measure of distress commonly used by general practitioners and in mental health settings, would be a useful tool to monitor mental health within the app. Self-monitoring mental health using mobile apps is an established effective method to increase emotional self-awareness [25]. Four general health and wellbeing questions will also be provided to prompt self-reflection regarding whether users are on track across four domains: mood, relationships, physical health, and productivity. In the absence of an evidence-based self-tracking tool, the four general health questions were codeveloped through consensus discussions with the project lead (LB) and mental health stream leads (MO, CJ) and the health care worker advisory group. The goal was to

provide a simple, self-monitoring check-in option that could be completed as often as a user chose.

In addition to self-monitoring tools, the app will include the 4-item Patient Health Questionnaire (PHQ4) as a measure of symptom burden, functional impairment, and disability. The PHQ4 comprises the 2-item Patient Health Questionnaire (PHQ2) for depression and the Generalized Anxiety Scale-2 (GAD2) as brief, validated subscales [26]. These questionnaires will help to establish a baseline of the mental health needs of the health care workers (eg, impact evaluation question 1) and will be used to identify any changes to these needs during and post app use (eg, impact evaluation question 3).

RMHive Development, Beta Testing, and Refinement

A co-design workshop will be conducted by the app developer and industry partner, Curve Tomorrow, using HCD principles and building on the data collected from the preparatory scoping interviews, needs analysis, and content creation stages. This workshop will lead to a clickable prototype of RMHive that will be used to gather additional user feedback prior to the beta test version of the app. Curve Tomorrow will gather telephone feedback from health care workers about the clickable prototype to generate the beta test app version. The beta test version will be released to one hospital unit (the emergency department), and feedback from users will inform the refinements that are needed for the implementation of the MVP for release for health care worker use hospital-wide.

Think aloud interviews [27] will be conducted with a subsample of users during the beta testing to inform refinements and identify bugs and required fixes. Think aloud interviews are commonly used to test new products and technologies, as simulated situations, and to enable a user to express their thoughts and feelings out loud as they use the app in real time [28]. The think aloud interviews will be audio- and video-recorded, and the outcomes will be summarized for beta test changes and reported in the impact evaluation. Key themes related to usability and perception of the content will be explored. An opt-in process to participate in the think aloud interviews will be employed.

App Architecture

RMHive will be designed to be a stand-alone app and will not be integrated into existing data repositories, human resource records, or electronic medical records. The RMHive app will be developed using the Ionic app development framework with a Rails backend and will function on iOS and Android operating systems. The app will be hosted via the secure cloud application platform Heroku. Data entered within the app will be anonymous to the research team, and only deidentified data will be provided to the research team for analysis. In the Terms of Use, app users will be asked to provide consent for the research team to contact them for think aloud interviews and collect data for the impact evaluation. It is planned that RMHive will be incorporated as a stand-alone resource into the well-being programs and policy response at RMH as one of a suite of support options for health care workers. Industry best practice standards for personal health information and data security will be followed. Data will be kept secure using industry-standard encryption over the wire

and at rest. Regulations to host data in Australia will be followed, and data security measures will comply with the Open Web Application Security Project's health care guidelines, the Australian Privacy Act, the ISO AS/NZ 27001, ISO AS/NZ 27017, and ISO AS/NZ 27018 standards, and SOC 2. The outcome paper will present a more detailed architecture in accordance with guidelines for reporting of health interventions using mobile phones [29].

Implementation

The RMHive app will be implemented for use by health care workers hospital-wide. An implementation strategy will be developed to guide the wider hospital release, and the effectiveness of this strategy in supporting the engagement, adoption, integration, and future sustainability of the app into individual work and organizational culture will be reported on in the impact evaluation. A 12-week impact evaluation period has been set following the release of the MVP to assess its uptake, engagement, use patterns, and impacts on mental health. This includes an assessment of the implementation enablers and challenges and the integration of data from the design and development stages that will inform the three impact evaluation questions.

Participants and Eligibility

Health care workers in the emergency and cardiology departments will participate in the preparatory phase, the adaptive governance structures and frameworks, and the planned design and development processes. Up to 30 health care workers will provide photo interview data and participate in deliberative workshops (including subsequent developer-conducted co-design workshops), and up to 15 health care workers will participate in think aloud interviews to inform the beta test. Governance interviews will be completed by up to 30 managers and leaders through the hospital. For wider release and implementation, all health care workers at RMH will be able to access the app and download it for use. Users will be provided an access code. In terms of understanding use and engagement with the app, 20% of health care workers who use the app for at least 7 to 30 days will be invited to participate in a think aloud interview. For the identification of the mental health needs of health care workers and the impact of the app use on their mental health, only data collected from the MVP stage will be included.

Sample Size

Up to 10,000 health care workers at RMH will have access to the RMHive app. Our sample size of app users is calculated based on an anticipated minimum rate of 10% of total staff downloading RMHive (n=1000). Of these users, 50% may go on to use the app (n=500), and of these, a further 50% are anticipated to cease using the app within the first 5 days (n=250). Of the 250 users remaining beyond five days, an additional 30% are anticipated to continue using the app for 7 days or more (n=175), and a further 50% of these users are likely to use the app for the full 30-day use period (n=87). These figures are based on download and use patterns reported in other health-related mobile apps [30].

Harms

Because the RMHive app development process will involve discussions and content about mental health and work challenges, there may be some risks to participant well-being. A protocolized participant distress response has been developed to support the needs of the participants, and study communications will provide avenues to national and institutional support services. Although RMHive is being developed to support the mental health of health care workers, the MVP is not a clinical or triaging tool, and it will not be developed to treat clinically determined symptoms of mental illness for this stage. Participants will be informed of this and will be encouraged both within the app and in study communications to seek further professional help if they feel their mental health and well-being needs warrant it. Some of the messages and advice within the app will be tailored to mental health screening outcomes (PHQ2 and GAD2) and provide directions to seek assistance where warranted. Recommended actions for the K10 results for self-monitoring will be included to guide access to professional support services. Support information will be made available in study communications through the research and development process and within the app.

Impact Evaluation Procedure

Conceptual Framework

The RMHive development process will use EBCD concepts to embed the lived experience of health care workers within the app content and features and will use adaptive governance frameworks to share power arrangements and decision-making in the co-design and implementation of the app. This means that health care workers will be embedded at all stages and processes of development. It is anticipated that the integration of health care worker perspectives using an EBCD and adaptive governance approach will increase the engagement and ongoing use of the RMHive app and subsequently lead to sustainability for organizational use. Additionally, developmental processes that seek to engage and understand organizational governance efforts will increase the ability to present RMHive as a key component of the health and well-being strategy across the organization. The success of this integration and support from governance stakeholders will be evaluated with attention to the adaptive governance framework underpinning the research collaboration [19].

Impact Evaluation Questions

The three impact evaluation questions are outlined again in [Table 1](#) alongside the data sources to inform these questions and the reporting or analytical framework proposed to answer the question. Further explanations of the planned analyses for the data sources are then described.

Table 1. Impact evaluation questions, data sources, and planned analyses.

Impact evaluation question	Data sources	Analytical focus or framework
1. What is health care workers' engagement with RMHive, including use patterns, perceptions of content, and overall level of engagement?	<ul style="list-style-type: none"> Change log from beta testing to the minimally viable product User demographics and mental health baseline measures (PHQ4^a, PHQ2^b, GAD2^c, K10^d self-monitoring and general health self-tracking questionnaires) App analytics data (bounce rates and patterns of use, including total time using and content use) Qualitative think aloud semistructured interview text and video data from the beta test and implementation phase 	<ul style="list-style-type: none"> Descriptive overview of beta test engagement and content changes Descriptive statistics on user demographics (age, gender, profession), mental health baseline scores and averages, K10 first completion averages Number of app downloads, use patterns, content accessed; patterns of content engaged with, number of videos watched, time spent on content (where possible) Thematic analysis of think aloud interview text content examining user perceptions of the app and content and video analysis for app usability and feature engagement (attention to facial gestures, body language, and user workflow); these data will be considered against the touchpoints identified in the photo interviews and deliberative workshops to evaluate the question of whether the app meets the needs of health care workers
2. What contextual, sociotechnical, organizational, and individual features support or hinder implementation of the RMHive app?	<ul style="list-style-type: none"> Qualitative governance interview data with leaders in the hospital setting Touchpoints that emerged from the photo interviews and deliberative workshops during design and development that were related to contextual, sociotechnical, organizational, and individual barriers and facilitators for implementation; review of available mental health and well-being programs at the hospital Qualitative think aloud semistructured interview text and video analysis Web-based implementation survey of team leaders, managers, and other appropriate staff distributed via hospital contacts 	<ul style="list-style-type: none"> NPT^e using the four NPT constructs to code interview, mapping, and brief survey data according to coherence (understanding of the problem—how people make sense of the mental health needs and well-being of health care workers, and the role of a mobile app in providing support), cognitive participation (engagement—how is the new technology driven forward, who buys in to it, and how is practice sustained), collective action (integration of new technology, skill set fit, integration of new technology, work done to operationalize and contextually execute new technology), and reflexive monitoring (how do groups and individuals start to assess whether a new approach or practice is working and what reconfigurations are undertaken by them to embed change) Identification of themes at the different levels in the qualitative interview data and deliberative workshop related to what supports or hinders app implementation and integration; these will also be mapped to NPT where appropriate Summary findings from a brief survey of managers and team leaders regarding the implementation of the mobile app
3. What are the identifiable impacts on the mental health of individual health care workers through adoption, implementation, and use of the RMHive app?	<ul style="list-style-type: none"> User demographics and mental health post-app use measures of depression, anxiety, and overall PHQ4 mental health score Self-monitoring data using K10 for psychological distress General health self-tracking questions: physical activity, relationships, productivity, and well-being 	<ul style="list-style-type: none"> Age, gender, and professional role where available; pre-PHQ2, GAD2, and overall PHQ4 scores compared with post-app use scores (defined as 30 days or last mental health entry on screening questionnaires) K10 self-monitoring scores at the first time of app use and last user completion First and last entries of self-tracking general health questions Case studies of patterns for K10 and the four general questions for further exploration of user mental health patterns over time if relevant

^aPHQ4: 4-item Patient Health Questionnaire.

^bPHQ2: 2-item Patient Health Questionnaire.

^cGAD2: 2-item Generalized Anxiety Scale.

^dK10: Kessler Psychological Distress Scale.

^eNPT: normalization process theory.

Data Analysis Plan

Use Patterns (Impact Evaluation Questions 1 and 3)

Participation rates (eg, total app downloads and bounce rates) and demographic summaries of age, gender, and profession will be provided using descriptive statistics. User analytics will be described in terms of time using the app; engagement with video content (yes or no responses to whether content was helpful); frequency of accessing individual elements of the app; time spent watching video content; links to mental health support services; and number of uses within the evaluation period. The presentation of the technological aspect of RMHive development and implementation will follow the mobile health evidence reporting and assessment (mERA) reporting guidelines [29]. The user analytics overview is presented in the supplementary table in [Multimedia Appendix 1](#).

Engagement With the App, Perceptions of Content, and Meeting Mental Health Needs (Impact Evaluation Question 1)

The photo interview and deliberative workshop text will be thematically analyzed using the Braun and Clarke approach, a theoretically flexible analysis method for qualitative data that draws out common patterns from data that relate to research questions [31]. This will enable themes related to mental health need identified in the needs analysis to be noted and considered against themes that may emerge from the discussion of use and content in the think aloud interviews through the beta testing and implementation of the MVP. Video analysis will examine body language, facial expressions, and discomfort or comfort with the use of the app to explore engagement with the app. Voice tone will be considered for user engagement.

Contextual, Sociotechnical, Organizational, and Individual Factors Affecting Implementation (Impact Evaluation Question 2)

The dynamic influence of contextual, sociotechnical, organizational, and individual factors and their impact on the implementation and engagement with RMHive will be assessed using normalization process theory (NPT) [32] and the mERA reporting guidelines [29]. NPT is an implementation science theoretical framework that is used to evaluate the success of implementation through a focus on actions rather than on beliefs or intentions [32]. NPT comprises four key constructs: coherence, which relates to the level of understanding people have about an intervention and the ways they make sense of new practices or technologies; cognitive participation, which describes the level of engagement and commitment people have to an intervention and the ways in which they start to embed or sustain a new practice or technology; collective action, which explores how well an intervention integrates with an organization's goals and activities, sociotechnical workflows, and compatibility with existing practices; and reflexive monitoring, which relates to engagement in the appraisal and monitoring of the intervention and outcomes, including the extent to which individuals and groups reconfigure their practice to sustain new practices or technologies [33]. The NPT framework will be applied specifically to the governance interview content, the brief implementation survey, and the

assessment of the implementation strategies developed for the MVP release. If relevant contextual or organizational themes are identified from the photo interviews and the beta test phase think aloud interviews, these will also be coded to the NPT constructs to support this analysis. Implementation leads (managers, team leaders, and health care worker members of the project team) will be provided with a link to a web-based survey to identify their awareness of RMHive, their use of the app, and any notable barriers or challenges that they have experienced. The facilitators and barriers of RMHive uptake will be examined at an individual level through engagement with app users and at an institutional level through ongoing governance interviews with respondents in management roles within RMH and the broader sociocultural context. mERA will be used to describe further technical implementation [29].

Impact on Mental Health (Impact Evaluation Question 3)

The impact evaluation will examine the profile of health care workers using RMHive, how RMHive is being used by health care workers through user analytics, and how the self-reported mental health of health care workers changes over the evaluation period.

On using the app for the first time, RMHive users will be prompted to establish a user profile and enter baseline data, including the PHQ4, which includes the PHQ2 and GAD2 subscales. The RMHive app will capture broad demographics, including age range; gender; whether the person is in a leadership position; and broad professional group (allied health; medical; nursing; administrative; environmental services; other). Additionally, users will be prompted to enter subjective general health ratings of their mood, physical health, productivity, and relationships on a 3-point scale (on track; neutral; not on track). Descriptive statistics will be used to summarize the sociodemographic and professional characteristics of the participants, their mental health responses, and subjective ratings collected at baseline and the last completed measure. For continuous data with a skewed distribution, medians and quartiles will be used instead.

The PHQ4 [26] will be the primary study outcome as an indicator of symptom burden, functional impairment, and disability, and RMHive users will be prompted to complete the PHQ4 at baseline, day 14, and day 28. The PHQ4 consists of the GAD2 anxiety subscale and the PHQ2 depression subscale. The PHQ2 assesses the presence of symptoms of depression over the last two weeks using a 4-point Likert scale (0, not at all; 1, several days; 2, more than half the days; 3, nearly every day). Total scores are calculated by summing the two items and can range between 0 and 6. The GAD2 assesses the presence of generalized anxiety symptoms over the past two weeks using a 4-point Likert scale (0, not at all; 1, several days; 2, more than half the days; 3, nearly every day). GAD2 has also been determined to indicate posttraumatic stress. Scores above 3 on each subscale will indicate symptoms of depression or anxiety [26,34,35]. The results of the two subscales will be reported individually and then summed to generate a PHQ4 score that can range from 0-12, with higher scores indicating an increased likelihood of underlying depressive or anxiety disorder.

Users will be provided with access to the 10-standard-item Kessler Psychological Distress Scale (K10) for self-monitoring upon completing their profile in the RMHive app [24]. Respondents will be asked to indicate how often in the past four weeks they have experienced certain symptoms (eg, nervousness, hopelessness, fatigue, agitation, and depressed mood) using a 5-point Likert scale (1, not at all, to 5, all the time). The total K10 score is the sum of the 10 items, ranging from 10-50, where higher K10 scores indicate greater higher psychological distress. If one item on the K10 is missing a response, the missing values will be substituted with the mean response of the completed items; otherwise, the total score will be coded as missing. Users will be able to self-monitor their emotional state at any time and will receive reminder prompts on day 2, day 5, and then weekly through app use. Completion of the K10 will be optional throughout the study, and users will be asked about the benefits or drawbacks of having access to the K10 for self-monitoring in the think aloud interviews for the wider release. K10 results will be reported using first and last completion of the measure by users. Subanalyses will be explored based on developing user case studies to examine over-time outcomes and self-monitoring trajectories.

Primary analysis will involve repeated measures analysis of covariance of the PHQ4 and subscale scores from baseline to day 14 and day 28. For users who only have baseline data, this analysis will be used to inform the question of the overall mental health need of health care workers. For users who enter data at baseline and again at both day 14 and day 28 or on either day, these time points will be reported as baseline, middle, and post use. For users with only two completed PHQ4 scores, these scores will be reported as pre and post. The analysis will progress with the existing data at each time point. For the secondary analysis, linear regression will be used to estimate the difference in the mean change from baseline in the mean K10 emotional state tracking and last use of K10.

Data Handling

Deidentified data with unique record identifiers for each participant will be extracted from the data collection system in the form of comma-separated value (CSV) data files. All research data will be stored in a deidentified format and will only be accessible to named research team members involved in the analysis process approved by the ethics committee. Data transfers from the app to the evaluation team will be conducted weekly during the beta test and following the MVP release as CSV files. The project manager will then download the CSV data files and will save the dummy-coded files to the central password-protected university system, where they will be stored securely and backed up regularly. Aggregate user analytics will be extracted using Firebase, and queries will be analyzed through Google Analytics and exported to CSV files for reporting and analysis. The data manager will then import the CSV files into Stata 15 (StataCorp LLC) [36] for data processing and statistical analysis. Data will be checked to identify errors and, where possible, resolve them before the analyses are conducted. Steps will include labelling the variables and values, creating composite variables, and creating the total scores according to the instrument's guidelines. Data sets will be merged using the unique identifier generated for each

participant. Deidentified data will be stored on password-protected university servers with access limited to the research team for future use in accordance with the National Statement on Ethical Conduct in Human Research [37].

Results

The RMHive program of work received funding in June 2020 and institutional ethics approval on June 9, 2020. Governance structures and committees were implemented in June, and data collection commenced in July. The impact evaluation will continue from design, development, and implementation up to mid-February 2021. It is anticipated that the study outcomes will be published in mid-2021.

Discussion

The adverse impact of pandemics on the mental health of health care workers has been well established [2,3], and prior research has established that mental health supports that address the needs of health care workers are required [13]. To date, the majority of mental health support tools for health care workers addressing pandemics have not incorporated the lived experience of end users in their development or implementation [13]. This may be a reason for the limited uptake and engagement with mobile apps. Mental health support tools developed and deployed in a compressed time frame and without an understanding of the lived experience of health care workers and their mental health needs carry an increased risk of not being delivered in a format that is readily accessible, desired, or ultimately used by health care workers. RMHive seeks to address these risks by using EBCD to support clinicians and researchers working together in a process of shared decision-making and co-design, leading to an app that centers the lived experience of health care workers as a basis for responding to their mental health needs [10]. This further extends the HCD approach to ensure active co-design by people with lived experience and shared power.

The RMHive app will be further supported by an impact evaluation that will provide critical insights into the contextual, sociotechnical, organizational, and individual factors that contribute to its implementation, engagement, and use. The impact evaluation [38] will expand current digital health frameworks by providing new insights into how EBCD processes inform the design, development, and implementation of an app directed toward addressing the mental health needs of health care workers. In keeping with the impact evaluation method, a theory of change will be produced from the evaluation to inform the future rollout and wider use of the app as a possible mental health and well-being intervention or support program. The impact of RMHive on the mental health outcomes of health care workers will also be assessed. It is recognized that in this evaluation, we are only focusing on near impacts of the RMHive app within the implementation context, and it is possible that the evaluation timeframe may not be sufficient for longer-term individual- and organizational-level changes to be observed.

To our knowledge, RMHive is the first mobile app developed using EBCD to support the mental health of health care workers

in response to a pandemic. It is hoped that RMHive will be a valuable support through the COVID-19 pandemic for health care workers who are experiencing increased challenges to their mental health and well-being. The impact evaluation outcomes will provide a valuable addition to local and international efforts

to support the mental health of health care workers through the deployment of digital mental health tools that can be rapidly co-designed and scaled in response to major events such as a global pandemic.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Supplementary table: overview of the user analytics plan.

[[DOCX File, 13 KB - resprot_v10i3e26168_app1.docx](#)]

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Abbreviations

COVIDDA: COVID Digital Asset
CSV: comma-separated value
EBCD: experience-based co-design
GAD2: 2-item Generalized Anxiety Scale
HCD: human-centered design
K10: Kessler Psychological Distress Scale
mERA: mobile health evidence reporting and assessment
MVP: minimally viable product
NPT: normalization process theory
PHQ4: 4-item Patient Health Questionnaire
PHQ2: 2-item Patient Health Questionnaire
RMH: Royal Melbourne Hospital

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Protocol

Mobile App-Based Intervention for Pregnant Women With Stress Urinary Incontinence: Protocol for a Hybrid Effectiveness-Implementation Trial

Tiantian Li^{1,2}, MD; Xiaomin Chen¹, MD; Jia Wang^{1,2}, MD; Ling Chen¹, PhD; Wenzhi Cai^{1,2}, PhD

¹Department of Nursing, Shenzhen Hospital, Southern Medical University, Shenzhen, China

²School of Nursing, Southern Medical University, Guangzhou, China

Corresponding Author:

Wenzhi Cai, PhD

Department of Nursing

Shenzhen Hospital

Southern Medical University

Number 1333, Xinhua Road

Baoán District Shenzhen, Guangdong

Shenzhen, 518101

China

Phone: 86 13078484316

Email: caiwzh@smu.edu.cn

Abstract

Background: Stress urinary incontinence (SUI) is a common source of distress among women during and after pregnancy. It has a negative effect on quality of life but with poor care-seeking. Mobile health (mHealth) may be a promising solution with potential advantages. However, there is uncertainty whether a mobile app is effective for SUI symptom improvement during and after pregnancy. The implementation is also unclear. We developed an app named UIW (Urinary Incontinence for Women) aimed at improving perinatal incontinence.

Objective: The objective of this study is to evaluate the effectiveness of the UIW app-based intervention in improving SUI symptoms among pregnant women and explore the facilitators and barriers to using the UIW app to help refine and optimize the intervention.

Methods: This study is a hybrid effectiveness-implementation trial with a randomized controlled trial alongside a mixed-methods process evaluation according to the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework. Pregnant women with SUI (n=336) will be recruited from a university-affiliated hospital in China. They will be randomly allocated (1:1) to either the intervention group that receive usual care plus UIW app or control group that receive usual care alone. The intervention period will last 2 months. The 5 dimensions of the RE-AIM framework will be evaluated at recruitment (-T1), baseline (T0), immediately after intervention (T1), 42 days after delivery (T2), 3 months after delivery (T3), and 6 months after delivery (T4) through project documents, online questionnaires and a pelvic floor muscle training diary, surface electromyography, log data in the background management system, and qualitative interviews. Data analysis will follow the intention-to-treat principle. Descriptive statistics, *t* tests, chi-square tests, and a linear mixed model will be used to analyze the quantitative data. Deductive and inductive content analysis will be used to analyze the qualitative data.

Results: The effectiveness-implementation trial started in June 2020, trial recruitment was completed in October 2020, and the intervention will last for a 2-month period. Completion of the 6-month follow-up will be in July 2021, and we anticipate that the results of this study will be published in December 2021.

Conclusions: This study will evaluate both effectiveness and implementation of the UIW app-based intervention among pregnant women. The hybrid effectiveness-implementation trial design according to the RE-AIM framework with a mixed-methods approach will give valuable insights into the effects as well as facilitators and barriers to the implementation that will influence the effects of the UIW app-based intervention.

Trial Registration: Chinese Clinical Trial Registry ChiCTR1800016171; <http://www.chictr.org.cn/showproj.aspx?proj=27455>

International Registered Report Identifier (IRRID): PRR1-10.2196/22771

KEYWORDS

mHealth; stress urinary incontinence; pregnancy; randomized controlled trial; process evaluation; mixed methods; study protocol

Introduction

Background

Stress urinary incontinence (SUI) is the most prevalent type of urinary incontinence (UI) accounting for half of women suffering from UI [1,2]. SUI is defined as the complaint of involuntary urine leakage on effort or physical exertion (eg, sports activities) or during sneezing or coughing [3]. Pregnancy and childbirth are regarded as the major predisposing factors of SUI [4]. About 40% of women experience SUI during pregnancy [5], and the prevalence of SUI after delivery is over one-fifth of women [6]. Other types include urgency UI, which is characterized by involuntary urine leakage with a strong desire to urinate, and mixed urinary incontinence, which is the combination of SUI and urgency UI [7]. UI negatively affects women's activities of daily life, mental well-being, and quality of life [8-10].

Pelvic floor muscle training (PFMT) is the first-line therapy for SUI, and the National Institute for Health and Care Excellence recommends women perform PFMT, especially during pregnancy [11]. Despite the availability of this effective therapeutic option for SUI, less than 30% of women seek help from health care professionals [12,13]. The reasons for not seeking treatment are multifaceted, such as embarrassment, stigma, insufficient knowledge, and perception of SUI among pregnant women [14]. Besides, a shortage of obstetric health care professionals and time restrictions during appointments also impede the delivery of perinatal incontinence care [15]. Given the unoptimistic condition, effective strategies are urgently needed to overcome these barriers. With the rapidly evolving development of information and communication technologies, mobile health (mHealth) may be a novel and promising strategy to improve perinatal SUI care [16].

mHealth is defined as achieving health objectives using mobile devices, such as mobile phones and other wireless devices [17]. With the advantages of anonymity, convenience, flexibility, and information support of mHealth, barriers to delivering perinatal incontinence care are lowered [18]. Women feel like they have greater privacy, are less embarrassed, have greater self-awareness of SUI, and appreciate the easy access to treatment options for SUI [19,20]. Moreover, 89% of the Chinese population use mobile phones, with a high prevalence of mobile internet usage in 2019 [21]. Thus, mHealth offers enormous potential to deliver SUI care to women on account of its advantages and high accessibility [16].

Several studies have proven mHealth to be effective for SUI management among community-dwelling women [22,23]. However, studies investigating the utility for mHealth to improve SUI symptoms during and after pregnancy are scarce [24]. Only one study was conducted with primiparas women [25]. Regrettably, it showed no significant difference in SUI symptoms between the mobile app-based intervention group

and control group, and the reasons for the less-than-optimistic results were underexplained. The most recent Cochrane systematic review also revealed that the effect of antenatal PFMT as a treatment for UI in incontinent women is uncertain [26], which arose from poor reporting of the control arm and process details in the study [27]. Moreover, pregnant women's use patterns and facilitators and barriers to using the app, referred to as process evaluation, should be explored further, which may explain variations in the success of mHealth interventions [28,29].

We developed a mobile app named UIW (Urinary Incontinence for Women) through an iterative and user-centered approach targeting pregnant women to improve perinatal incontinence care. It is an evidence-based and theory-driven app containing multiple intervention components based on the input of important stakeholders' perspectives (pregnant women, obstetricians, and nurses). Therefore, we will assess the effectiveness and implementation of the UIW app, as adopted by pregnant women, compared to usual care, in this study, using a hybrid effectiveness-implementation study design through mixed-methods research [30,31]. The results of this study will also contribute to updating the Cochrane review to determine the effect of antenatal PFMT as a treatment for UI.

Objectives

The overall goal of this effectiveness-implementation study is to provide more valuable insights into underlying reasons for the effective or ineffective results of app-based interventions among pregnant women with SUI compared to usual care. Then, it will provide a possibility to foster the implementation of an app-based intervention to improve incontinence care during and after pregnancy. There are 2 specific objectives in this study. First, we will evaluate whether the UIW app-based intervention is effective in improving SUI symptoms of pregnant women, as compared to usual care. Second, we will explore the facilitators and barriers to using the app during the implementation to help refine and optimize the intervention.

Methods

Study Design

This study is a hybrid type 1 effectiveness-implementation trial due to the need to determine the effectiveness of the UIW app-based intervention and understand the implementation to explain the effects of the intervention [30,31]. A randomized controlled trial (RCT) was designed to evaluate the effectiveness of the UIW app-based intervention compared to usual care among pregnant women with SUI, in parallel with an implementation research through a mixed-methods process evaluation following the explanatory sequential mixed-methods design (Figure 1) [32,33]. Reach, Effectiveness, Adoption, Implementation and Maintenance (RE-AIM) framework will be used to guide the evaluation, which is the vital evaluation theory on health promotion intervention [34,35].

This trial protocol has been developed in line with the Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and onLine TeleHealth (CONSORT-EHEALTH) guidelines (Multimedia Appendix 1) [36], Standard Protocol Items for Randomized Trials (SPIRIT

2013 statement (Multimedia Appendix 2) [37], and guidance for the qualitative research undertaken with the trial (Multimedia Appendix 3) [38]. The CONSORT flowchart is displayed in Figure 2.

Figure 1. An overview of the trial design for the UIW (Urinary Incontinence for Women) app trial. PFMT: pelvic floor muscle training; RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance; sEMG: surface electromyography; -T1: recruitment period; T0: baseline; T1: immediately after intervention; T2: 42 days after delivery; T3: 3 months after delivery; T4: 6 months after delivery.

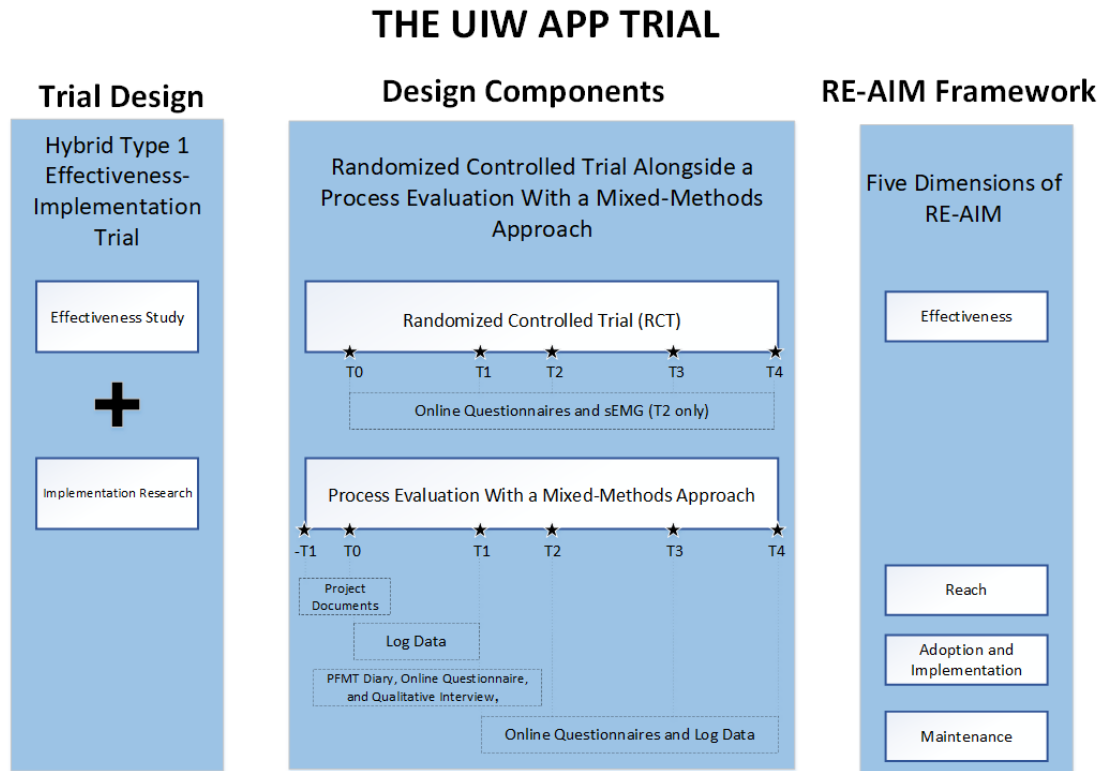
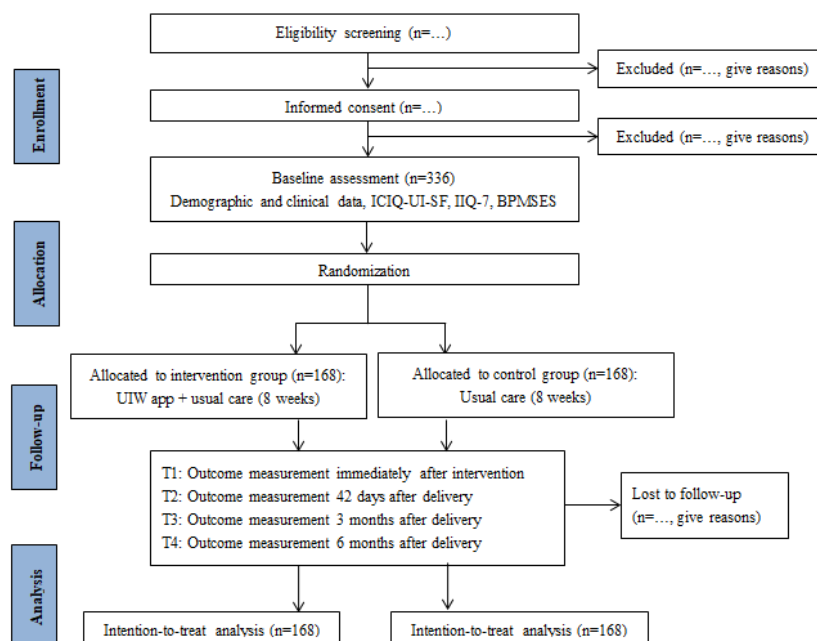


Figure 2. Trial flowchart according to CONSORT (Consolidated Standards of Reporting Trials). BPMSES: Broome Pelvic Muscle Self-Efficacy Scale; ICIQ-UI-SF: International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form; IIQ-7: Incontinence Impact Questionnaire-7; UIW: Urinary Incontinence for Women; T1: immediately after intervention; T2: 42 days after delivery; T3: 3 months after delivery; T4: 6 months after delivery .



Setting

The study will be conducted in Shenzhen Hospital, Southern Medical University, a university-affiliated, tertiary level-A, public hospital in China. An average of 2000 pregnant women per month receive routine antenatal assessments in the hospital, and a vast majority of these pregnant women have access to a mobile phone and the internet [21].

Eligibility of Participants

Inclusion Criteria

Pregnant women will be eligible if they are at least 18 years of age, have a singleton pregnancy according to ultrasonographic evaluation, are at 24-28 gestational weeks, have access to a mobile phone and the internet, and have SUI symptoms with ≥ 1 leakage episodes over the past 4 weeks (SUI symptoms are assessed by asking the question “When does urine leak?”). The question is an unscored item in the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-UI-SF), which has good reliability and validity [39]. SUI is defined as involuntary urine leakage on effort or physical exertion (eg, sports activities) or during sneezing or coughing [3]).

Exclusion Criteria

Pregnant women will be excluded if they have a psychiatric illness or cognitive impairment; previous UI; pelvic organ prolapse or pelvic surgery; or serious comorbidities or complications like heart disease, diabetes mellitus, hypertensive disorder of pregnancy, threatened abortion, placenta previa, placental abruption and premature rupture of membranes, fetal growth restriction, and amniotic fluid abnormalities.

Recruitment and Informed Consent

Eligibility will be assessed by the researchers (TTL and JW) by checking the medical records from the obstetrics clinic. The researchers (TTL and JW) will introduce the study verbally, provide an information letter about the study with contact details of the researchers to eligible pregnant women, and patiently answer their questions. Pregnant women have 3 days to consider if they want to participate in this study. After agreeing, written informed consent will be obtained from participants by the researchers (TTL and JW), and a baseline electronic questionnaire including demographic and clinical data will be completed at the same time. The pregnant women will be informed that if there is any discomfort or pain associated with PFMT, they should contact the researchers by telephone without

delay. The duration of enrollment is expected to cover a 3-month period. Pregnant women will be rewarded with a cash coupon (equal to RMB 150; US \$23.19) after completing the study.

Randomization and Blinding

The recruited pregnant women will be randomly assigned to either the intervention or control group with a 1:1 ratio using a simple randomization method. An independent research assistant will generate a random allocation sequence of 168 unique numbers using a random number table and write on different colored paper (pink paper for the first 168 numbers arranged in ascending order, white paper for the remaining numbers). This paper will be folded and put into consecutively numbered, sealed, opaque envelopes by the independent research assistant to conceal the allocations. The researchers (TTL and JW) will open the envelopes in numerical order during the process of recruiting and assigning participants. The participants with a pink paper will be assigned to the intervention group; others with a white paper will be assigned to the control group. The pregnant women in the intervention group will receive usual care plus the UIW app. The UIW app will be downloaded by scanning the QR code. The pregnant women in the control group will receive usual care alone.

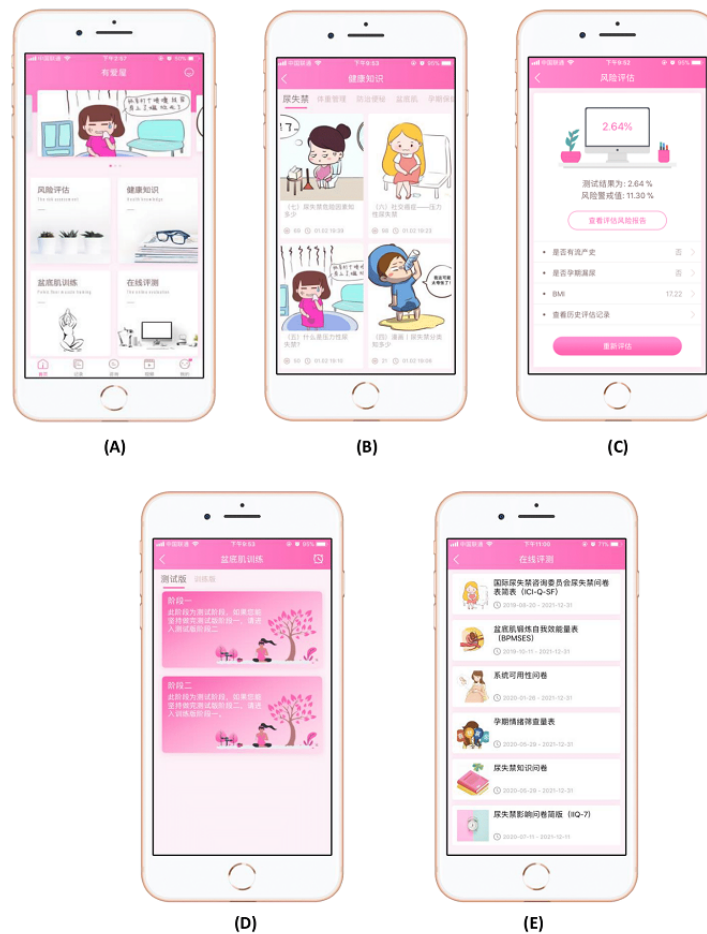
Due to the nature of the app-based intervention and self-reported outcomes, except the assessment of pelvic floor muscle strength using surface electromyography (sEMG), it is not feasible to blind the participants or most of the outcome assessments. The experienced obstetricians delivering usual care and performing the sEMG tests are independent from this study and have no conflict of interest. They provide all participants with the same care and will remain blinded to the group allocation.

Intervention

UIW App

The UIW app is a mobile app for Chinese pregnant women with SUI developed by a research team from Shenzhen Hospital, Southern Medical University with technical assistance from the Guangdong Zhuoshang Network Technology Company (Registration Number: 2019SR1342273). There are 4 major modules in the UIW app including the Risk Assessment forum, Health Knowledge forum, PFMT forum, and Online Evaluation forum, with the functions of education, reminders, self-monitoring, and others, all arising from behavior change techniques (Multimedia Appendix 4) [40]. The 4 modules are visibly placed on the home page of the UIW app (Figure 3).

Figure 3. Screenshots of the UIW (Urinary Incontinence for Women) app, including the (A) Home Page, (B) Risk Assessment forum, (C) Health Education forum, (D) Pelvic Floor Muscle Training (PFMT) forum, and (E) Online Evaluation forum.



The Risk Assessment forum provides a risk prediction for SUI during the early stage of pregnancy based on a predictive tool previously developed by the research team [41]. According to the pregnant woman's clinical risk factors, it identifies the high-risk population and gives feedback to the users whether they are at a high or low risk level.

The Health Education forum provides 5 topics specific to SUI and general pregnancy care, including SUI and lifestyle factors associated with SUI (weight management and constipation prevention [42,43], pelvic floor muscle care, and general antenatal care). A literature review, user needs analysis, and multidisciplinary expert group meeting were carried out to create the 5 topics.

The PFMT forum provides a personalized and instructional PFMT protocol adapted from the "Tāt-an internet-based intervention providing PFMT to treat SUI" [44]. The PFMT is ordered by increasing difficulty. It consists of 2 basic levels and 4 advanced levels including different combinations and repetitions of 4 commonly used contraction types: test contraction, strength contraction, endurance contraction, quick contraction. When performing PFMT, the app shows real-time, dynamic guidance in the form of columnar graphics that present the duration and intensity of pelvic floor muscle contraction with concomitant relaxation. Pregnant women follow the image and sound command to contract and relax the pelvic floor

muscles. Alarms can also be set to push notifications reminding the pregnant women to train.

The Online Evaluation forum provides reliable and validated questionnaires to evaluate the women's SUI severity, quality of life, and self-efficacy with PFMT.

Additionally, at the bottom of the home page, there are other functions including recording of behaviors in daily life, consulting health care professionals about SUI-related questions, watching videos related to SUI, managing personal information, and system setup. Driven by administrative and adherence-focused guidance, the app also provides technical support, adherence monitoring, and reminders sent by the background management system in case the UIW is not logged into within 7 days [45]. The intervention period will last 2 months because research evidence indicates that 8 weeks PFMT is enough to improve the symptoms of SUI [46]. During the intervention period, pregnant women will autonomously use the app; it is up to them to determine their usage pattern in terms of frequency and duration of use.

The researcher will assist pregnant women in the intervention group with downloading the UIW app, registering, and installing their accounts. The pregnant women will be free to set up their usernames and passwords to submit the account application. Once the researcher confirms submission through the background management system, their accounts will be

activated. The pregnant women will need to complete their personal information. Participants will be informed that the researchers have access to their profile.

A link to the electronic user manual and instructions for the UIW app will be fixedly displayed at the top of the home page. Technical support can be provided via the user manual and instructions on how to operate the UIW app. Moreover, the pregnant women can post their technology-related questions through the Assistance and Feedback function below the System Setup module. The researcher will respond to them within 24 hours.

Usual Care

The pregnant women in the intervention group and control group will both receive the same usual care. Usual care involves one-to-one health education about SUI and PFMT practice guidance at the time of recruitment by experienced obstetricians. It is delivered based on the Guidelines on the Medical Service Capacity of Tertiary Obstetrics and Gynecology Hospitals (National Health Commission of the People's Republic of China, 2017 edition) [47]. The health education is verbally provided, which covers information corresponding to the 5 topics in the Health Education forum of the UIW app. PFMT practice guidance is teaching the correct pelvic floor muscle contraction technique and confirmation by obstetricians of a correct contraction through perineum palpation with the pregnant women in the supine position. Women will be directed to be aware of the feeling of selectively contracting muscles surrounding the urethra, vagina, and anus while relaxing the abdomen and buttocks muscles. Meanwhile, obstetricians will put one hand on the perineal body and the other hand on the abdomen to identify if women can correctly contract and relax the pelvic floor muscles; participants will be encouraged to contract the pelvic floor muscles more than 100 times per day [26].

Measurements and Instruments of Data Collection

Overview

We will use a mixed-methods approach to evaluate the effectiveness and implementation of the trial according to the RE-AIM framework. Quantitative methods will be specifically used to measure the dimensions of Reach, Effectiveness, Adoption (UIW app usage results and patterns), Implementation, and Maintenance. For the Adoption dimension, qualitative methods will be used to explore the facilitators and barriers to adoption of the UIW app-based intervention from the pregnant women's perspective. [Multimedia Appendix 5](#) demonstrates the measures used in this study. Data will be collected at recruitment (–T1), baseline (T0), immediately after the intervention (T1), 42 days after delivery (T2), 3 months after delivery (T3), and 6 months after delivery (T4). Data will be collected from both the UIW app-based intervention group and control group. For the Reach dimension, the participation rate of eligible pregnant women will be examined using the project document data recorded by the researchers. For the Effectiveness dimension, there is 1 primary outcome, and there are 4 secondary outcomes, which are described in the following sections.

Primary Outcome

Symptoms of SUI will be evaluated using the ICIQ-UI-SF [48]. The ICIQ-UI-SF is a 4-item instrument with 3 scored items assessing the frequency of leakage, amount of leakage, and overall impact of leakage on life and 1 unscored item diagnosing the type of UI. The total score ranges from 0 to 21, with 0-7 indicating mild symptoms, 8-13 indicating moderate symptoms, and 14-21 indicating severe symptoms. The Chinese version of the ICIQ-UI-SF has a Cronbach α coefficient of 0.71 and over 95% agreement between the 2 tests [49].

Secondary Outcomes

The secondary outcomes include pelvic floor muscle strength, quality of life, self-efficacy with PFMT, and risk factors for SUI.

Pelvic floor muscle strength will be assessed using sEMG with the Vishee neuro-muscle stimulator (MyoTrac Infiniti, model SA9800, Thought Technology Ltd, Montreal, Quebec) [50]. It will be performed by following the Glazer protocol by 2 independent and experienced obstetricians who have passed the medical qualification examination and have more than 5 years of working experience. After participants are in a supine lithotomy position, a drop-shaped vaginal probe (registration certificate number: 20152211142, type VET-A, produced by Nanjing Vishee Medical Technology Ltd, Nanjing China) will be placed into the vagina. Participants will be instructed how to correctly contract the pelvic floor muscles to avoid crosstalk contamination of the surrounding muscles before starting the test. Then, participants will follow the text hints and voice prompts of the automated protocol software to contract and relax the pelvic floor muscles. The whole test includes 5 indicators of amplitude (μ V): pretest resting, phasic contraction, tonic contraction, endurance contraction, and posttest resting. A lower amplitude indicates weaker pelvic muscle strength. sEMG is a reliable way to measure pelvic floor muscle strength, and its values are closely related to SUI [51].

Quality of life among pregnant women with SUI will be assessed using the Incontinence Impact Questionnaire-7 (IIQ-7) [52]. The IIQ-7 is a 7-item instrument with 4 domains including physical activity, travel, social activities, and emotional health. Higher total score indicates a higher level of impact on life. The Chinese version of the IIQ-7 has a Cronbach α coefficient of 0.824 and high construct validity [53].

Self-efficacy with PFMT will be measured using the Broome Pelvic Muscle Self-Efficacy Scale (BPMSES) [54]. The BPMSES is a 23-item instrument with 14 items in the dimension of self-efficacy expectations and 9 items in the dimension of outcome expectations. A total score of 0-33 indicates low self-efficacy, 34-66 indicates moderate self-efficacy, and 66-100 indicates high self-efficacy. The Chinese version of the BPMSES has a Cronbach α coefficient of 0.912 and a test-retest reliability coefficient of 0.910 [55].

Risk factors for SUI among pregnant women will be assessed using a self-designed questionnaire, investigating weight, condition of constipation, active and passive smoking, and consumption of liquids containing caffeine.

For the dimension of Adoption, the pregnant women's PFMT adherence and activity in the 2 groups, usage results and patterns of use of the UIW app for the intervention group, other possible apps and websites used by the control group, and facilitators and barriers to adoption of the app will be explored through quantitative and qualitative methods. PFMT adherence and activity as well as usage results and patterns will be evaluated using quantitative methods through the log data of the background management system for the intervention group; a self-administered, electronic PFMT diary; and an electronic questionnaire (Multimedia Appendix 5). For the qualitative interviews, we will adopt a purposive sampling strategy to select women from the 2 groups based on the primary outcome of the SUI symptom score at the end of the intervention. Pregnant women will be selected at a ratio of 1:1 in the higher and lower scores until achieving data saturation such that no new themes emerge during data analysis. The interviews will be performed by a researcher (TTL) via telephone or face-to-face. The interviewer is a female nurse with a master's degree in nursing science and formal training in qualitative studies. A semistructured interview guide was developed by the research team and covers the topics of user experiences, preferences, and expectations (Multimedia Appendix 5). Data collection, management, and analysis will be carried out concurrently, which makes it possible to adapt and refine the interview guide [56]. All interviews were audiotaped after gaining permission from the participants.

For the dimension of Implementation, the fidelity of the intervention and usual care provided will be evaluated (Multimedia Appendix 5).

For the dimension of Maintenance, the measures used to assess "Effectiveness," "Adoption," and "Implementation" will be repeatedly assessed in the follow-up period at the T2, T3, and T4 time points.

Data Management and Analysis

Quantitative Data

To avoid bias due to unnecessary face-to-face contact, data for pregnant women in both the intervention group and control group are collected electronically, using app-based and internet-based methods, respectively. After the data are exported from the app's background management system and questionnaire website, data will be entered directly in a special database for the UIW app and saved in the database by researchers on a password-protected computer. Each participant is identified by a unique study ID assigned by the independent researcher assistant at the time of recruitment. And the "log" connecting the participants with the study IDs is held by the independent research assistant.

SPSS (version 25.0; IBM Corp, Armonk, NY) will be used for all quantitative data analysis. Descriptive statistics will be used to show continuous variables as mean (SD) and categorical variables as frequency and percentage. The baseline data will be compared between the intervention and control groups as well as between participants completing the follow-up of this study and those who drop out, with the independent sample *t* test for continuous variables and the chi-square test or Fisher

exact test for categorical variables. The effects of the intervention within each group will be assessed with a paired *t* test for the severity of SUI, quality of life, and self-efficacy with PFMT and a McNemar chi-square test for risk factors. To compare the effects of the intervention between groups for the repeated measures, including severity of SUI, quality of life, and self-efficacy with PFMT, a linear mixed model will be used, which allows for missing data [57]. The model will include subjects as random effects and time, intervention, and the interaction between intervention and time as fixed effects. Pelvic floor muscle strength will be compared between groups using an independent sample *t* test. For the risk factors and PFMT adherence, chi-square tests will be used to compare the differences between groups. *P* values <.05 will be considered statistically significant.

Participants with missing data will also be included in the analysis following the principle of intention-to-treat analysis. Missing data at follow-up will be replaced with the corresponding values at baseline.

Qualitative Data

The semistructured, in-depth interviews conducted by telephone or face-to-face will be transcribed verbatim into text by the researchers (TTL and JW) within 24 hours after the telephone interview. Qualitative data analyses will be performed using NVivo software (version 11; QSR International, Melbourne, Australia). We will apply deductive and inductive content analysis to analyze the transcripts. Two researchers will separately perform the initial coding. The codes will be checked for agreement, compared regarding the similarities and differences, and grouped into subcategories and categories to form subthemes and themes. Several techniques will be used to improve the trustworthiness of the qualitative study, including respondent validation, triangulation, peer debriefings, and audit trails.

Sample Size Calculation

The sample size calculation was based on the primary outcome of the SUI symptom score, which is used to estimate the effect size in the power analysis [58]. A previous mobile app-based study performed among primiparas women showed a moderate effect size (0.344) [25]. G*Power [59] was used to estimate the sample size. A minimum sample size of 268 pregnant women is required for this study to achieve a power of 0.80 at a 2-sided significance level of .05. A 20% attrition rate is estimated based on previous studies involving mHealth interventions [60]. The total sample size was increased to 336, with 168 in each group.

Ethical Approval

The study has received ethical approval from the Ethics Committees of Shenzhen Hospital, Southern Medical University (approval number NYSZYEC20190012) on August 27, 2019. It will be performed in accordance with Helsinki 1964 and later revisions and overseen by the independent trial steering committee (TSC) and data monitoring and ethics committee (DMEC). The TSC provides overall supervision for this research on behalf of the funder, and the DMEC reviews confidential interim analyses semiannually to monitor data, oversee trial safety and progress, and make recommendations. In addition,

all participants in this study will provide written informed consent and hold rights to withdraw from this trial in anytime. Participants' data will be anonymous and stored on a password-protected background management system. Any adverse events experienced by participants during this study will be recorded and reported to the DMEC.

Results

The effectiveness-implementation trial started in June 2020, trial recruitment was completed in October 2020, and the intervention will last for a 2-month period. Completion of the 6-month follow-up will occur in July 2021, and we anticipate that the results of this study will be published in December 2021.

Discussion

Research has indicated that a vast majority of pregnant women are expected to screen for SUI [61]. mHealth is a promising solution to improve SUI care during and after pregnancy. This study will provide valuable information on the effectiveness and implementation of the UIW app-based intervention aimed at improving SUI symptoms in women during and after pregnancy. By using a hybrid type 1 effectiveness-implementation trial, an extensive process evaluation with a mixed-methods approach will be performed alongside an RCT. Facilitators and barriers to the use of the UIW app-based intervention will also be explored. The results will provide a deep understanding of the underlying effect mechanism of the app-based intervention. This will contribute to better implementation and dissemination in the clinical context.

Previous studies were mostly aimed at community-dwelling women [22,23]. Only 1 study was performed among pregnant women but did not show significant effects [25]. The underlying reasons are unclear. To the best of our knowledge, this is the first study to evaluate an app-based intervention for SUI distress in pregnant women using a hybrid type 1 effectiveness-implementation trial design. If the UIW app-based intervention is effective, this study will provide evidence to improve perinatal incontinence care using a mobile app.

Strengths and Limitations

This study is powered by some strengths. First, the UIW app functions are comprehensive. It not only focuses on PFMT but also merges various behavior change techniques, including shaping knowledge, feedback, self-monitoring, and others [40]. Second, given the implementation of "Two-Child Policy" in China, the number of multiparas women is obviously increasing [62]. To evaluate the effectiveness of the UIW app-based intervention in a more realistic clinical context, we will enroll

both primiparas and multiparas women in this study. Third, a hybrid type 1 effectiveness-implementation design, with RE-AIM as the guidance framework, is applied in this study. The RE-AIM framework specifies multiple domains of evaluation [34] and has been commonly utilized in research on health promotion intervention [63]. Knowledge gained from this sophisticated design will make a great contribution to the RCT evaluating the mHealth intervention. Furthermore, integration of quantitative and qualitative methods will occur at various levels through the mixed-methods design of the implementation evaluation [32]. At the study design level, an explanatory sequential design is employed. In the qualitative study, interview samples will be purposely selected from the participants of the RCT according to the primary outcome. Thus, integration occurs through connecting and building at the methods level.

There are several potential limitations. One limitation may be that the sEMG will be only assessed at 42 days after delivery. Considering that an sEMG is conducted via a probe placed into the vagina, we will not assess sEMG during pregnancy due to the potential risk. Participants will seldomly return to the hospital after the reexamination at 42 days after delivery, and it is difficult to reach the participants. In view of feasibility and acceptability, the sEMG assessments will not also be conducted at 3 months and 6 months after delivery. Another limitation may lie in the requirements of having a mobile phone and access to the internet. It may lead to a more tech-savvy population who are more familiar and comfortable with mobile phone use and limit the generalizability to the whole population of pregnant women, although the rates of internet use and mobile phone ownership are relatively high. Finally, though the process evaluation is important to interpret the trial findings, it aims to provide transparency of the implementation of the intervention [64]. It only provides a possible explanation about the results rather than a full explanation.

Conclusions

Although mHealth is a promising technology, the effectiveness and implementation of mHealth interventions need to be explored. The UIW app is an evidence-based and theory-driven app containing a comprehensive set of functions. In this study, we will investigate the effectiveness of as well as facilitators and barriers to the implementation of the UIW app-based intervention among pregnant women. A hybrid effectiveness-implementation trial design according to the RE-AIM framework has been adopted, with an RCT conducted in parallel with a mixed-methods process evaluation. This study will expand the understanding of the app-based intervention to improve the SUI situation among pregnant women. Insights into the study results can enhance the implementation and dissemination of this intervention in the clinical context.

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for this research by the TSC on behalf of the funder and the independent DMEC that reviews our confidential interim analyses semiannually to monitor data, oversee trial safety and progress, and make recommendations.

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Final results will be disseminated to the funding bodies, peer-reviewed journals, international conferences, and relevant health care communities. And public access to the full protocol, dataset, and statistical code is available through the Chinese Clinical Trial Registry (ChiCTR).

Authors' Contributions

TL and LC conceived the study and were involved in the initial study design. XC, LC, and TL contributed to the development of the UIW app. TL and JW were involved with participant recruitment and data collection. TL completed the first draft of the manuscript. All authors contributed to reviewing the protocol and approving the final manuscript. WC and LC are the principal investigators and responsible for the overall management of this trial. The final trial dataset can be accessed upon request from WC and LC after study completion.

Conflicts of Interest

None declared.

Multimedia Appendix 1

CONSORT-eHEALTH checklist (V 1.6.1).

[\[PDF File \(Adobe PDF File\), 349 KB - resprot_v10i3e22771_app1.pdf\]](#)

Multimedia Appendix 2

SPIRIT 2013 checklist.

[\[PDF File \(Adobe PDF File\), 315 KB - resprot_v10i3e22771_app2.pdf\]](#)

Multimedia Appendix 3

Guidance for the qualitative research undertaken with trial.

[\[PDF File \(Adobe PDF File\), 245 KB - resprot_v10i3e22771_app3.pdf\]](#)

Multimedia Appendix 4

Mapping of the Behavior Change Techniques and elements in UIW app UIW: Urinary Incontinence for Women; PFMT: Pelvic Floor Muscle Training.

[\[PDF File \(Adobe PDF File\), 73 KB - resprot_v10i3e22771_app4.pdf\]](#)

Multimedia Appendix 5

List of measures. -T1: recruitment period; T0: baseline; T1: immediately after intervention; T2: 42 days after delivery; T3: 3 months after delivery; T4: 6 months after delivery.

[\[PDF File \(Adobe PDF File\), 481 KB - resprot_v10i3e22771_app5.pdf\]](#)

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Abbreviations

BPMSES: Broome Pelvic Muscle Self-Efficacy Scale

CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and onLine TeleHealth

DMEC: data monitoring and ethics committee

ICIQ-UI-SF: International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form

IIQ-7: Incontinence Impact Questionnaire-7

mHealth: mobile health

PFMT: pelvic floor muscle training

RCT: randomized controlled trial

RE-AIM: Reach, Effectiveness, Adoption, Implementation and Maintenance

sEMG: surface electromyography

SPIRIT: Standard Protocol Items for Randomized Trials

SUI: stress urinary incontinence

TSC: trial steering committee

UI: urinary incontinence

UIW: urinary incontinence for women

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Protocol

Beyond Getting Rid of Stupid Stuff in the Electronic Health Record (Beyond-GROSS): Protocol for a User-Centered, Mixed-Method Intervention to Improve the Electronic Health Record System

Ahmed Umar Otokiti^{1,2*}, MD, MBA, MPH; Catherine K Craven^{2,3*}, MA, MLS, FAMIA, PhD; Avniel Shetreat-Klein^{2,4}, MD, PhD; Stacey Cohen^{2,4}, PT; Bruce Darrow⁵, MD, PhD

¹Department of Medicine, Icahn School of Medicine at Mount Sinai, Mount Sinai Health System, New York, NY, United States

²Clinical Informatics Group, Information Technology Department, Icahn School of Medicine at Mount Sinai, Mount Sinai Health System, New York, NY, United States

³Institute for Health Care Delivery Science, Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, Mount Sinai Health System, New York, NY, United States

⁴Department of Rehabilitation and Human Performance, Icahn School of Medicine at Mount Sinai, Mount Sinai Health System, New York, NY, United States

⁵Department of Cardiology and Health Information Technology, Mount Sinai Health System, New York, NY, United States

*these authors contributed equally

Corresponding Author:

Ahmed Umar Otokiti, MD, MBA, MPH

Department of Medicine

Icahn School of Medicine at Mount Sinai

Mount Sinai Health System

1 Gustave L Levy Place

New York, NY, 10029

United States

Phone: 1 212 289 6393

Email: ahmedotoks@yahoo.com

Abstract

Background: Up to 60% of health care providers experience one or more symptoms of burnout. Perceived clinician burden resulting in burnout arises from factors such as electronic health record (EHR) usability or lack thereof, perceived loss of autonomy, and documentation burden leading to less clinical time with patients. Burnout can have detrimental effects on health care quality and contributes to increased medical errors, decreased patient satisfaction, substance use, workforce attrition, and suicide.

Objective: This project aims to improve the user-centered design of the EHR by obtaining direct input from clinicians about deficiencies. Fixing identified deficiencies via user-centered design has the potential to improve usability, thereby increasing satisfaction by reducing EHR-induced burnout.

Methods: Quantitative and qualitative data will be obtained from clinician EHR users. The input will be received through a form built in a REDCap database via a link embedded in the home page of the EHR. The REDCap data will be analyzed in 2 main dimensions, based on nature of the input, what section of the EHR is affected, and what is required to fix the issue(s). Identified issues will be escalated to relevant stakeholders responsible for rectifying the problems identified. Data analysis, project evaluation, and lessons learned from the evaluation will be incorporated in a Plan-Do-Study-Act (PDSA) manner every 4-6 weeks.

Results: The pilot phase of the study began in October 2020 in the Gastroenterology Division at Mount Sinai Hospital, New York City, NY, which includes 39 physicians and 15 nurses. The pilot is expected to run over a 4-6-month period. The results of the REDCap data analysis will be reported within 1 month of completing the pilot phase. We will analyze the nature of requests received and the impact of rectified issues on the clinician EHR user. We expect that the results will reveal which sections of the EHR have the highest deficiencies while also highlighting issues about workflow difficulties. Perceived impact of the project on provider engagement, patient safety, and workflow efficiency will also be captured by evaluation survey and other qualitative methods where possible.

Conclusions: The project aims to improve user-centered design of the EHR by soliciting direct input from clinician EHR users. The ultimate goal is to improve efficiency, reduce EHR inefficiencies with the possibility of improving staff engagement, and lessen EHR-induced clinician burnout. Our project implementation includes using informatics expertise to achieve the desired state of a learning health system as recommended by the National Academy of Medicine as we facilitate feedback loops and rapid cycles of improvement.

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KEYWORDS

electronic health records; burnout, psychological; user-centered design; usability; EHR optimization

Introduction

Background

Substantial evidence indicates that electronic health records (EHRs) contribute greatly to clinician burnout [1-5]. This burden arises from factors like EHR usability or lack thereof, perceived loss of autonomy, and documentation; this leads to less clinical time with patients and clinicians creating various workarounds to the problem with the associated potential to compromise execution of care consistent with patient safety and quality [1,6]. Clinician burnout and dissatisfaction can adversely impact provider engagement, which in turn, can negatively impact patient safety and health care quality [7,8].

In an effort to alleviate the EHR burden imposed on clinicians and its adverse consequences on the quality of health care delivery, Hawaii Pacific Health implemented a program called Getting Rid of Stupid Stuff (GROSS). In this program, clinicians were asked to come forward with anything in the EHR that they thought was poorly designed, unnecessary, or just “plain stupid” [9].

This protocol is a description of how we plan to implement a modified and extended version of the Hawaii Pacific Health system's GROSS program in our medical center at Mount Sinai Hospital in New York City, NY. Our program will be called Beyond Getting Rid of Stupid Stuff (Beyond-GROSS).

Hawaii Pacific Health GROSS Experience

Hawaii Pacific Health is the largest private health care organization in Hawaii with 4 medical centers, 592 beds, 6950 staff, and 1764 physicians [10]. The GROSS program seeks direct input from clinicians about various aspects of the EHR and documentation that is not useful or counterintuitive.

Categories of requests received included the following: documentation that was never meant to occur and would require little consideration to eliminate or fix, documentation that was needed but could be completed in a more efficient or effective way with newer tools or better understanding, and

documentation that was required but for which clinicians did not understand the requirement or tools available to them.

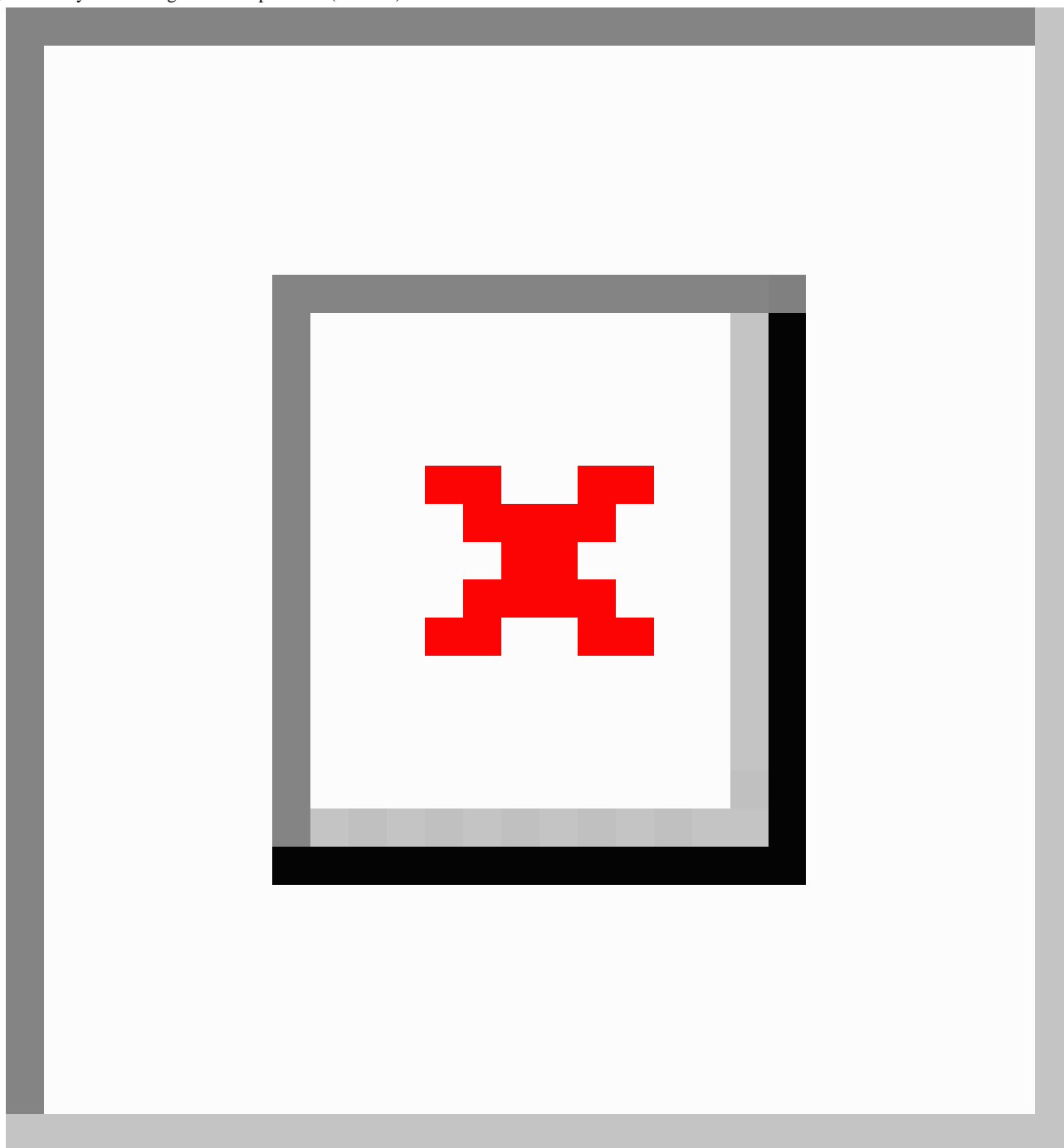
After 1 year of implementation, a total of 188 requests were received in all 3 categories by the GROSS team. Suggestions from other disciplines were not presented. Also, suggestions related to issues other than EHR improvement were not permitted [9].

The results showed the following: There were more responses from nurses (n=146) than physicians (n=42), the vendor (Epic EHR) was supportive of the effort, there was an overall organizational acceptance of the project by clinicians, and there were minor changes in the EHR based on suggestions from users. Data about physician engagement were pending at the time of publication.

Mount Sinai Beyond-GROSS Program Objectives and Justification

The issue of burnout and clinician engagement is now a widespread concern among all stakeholders, including government and expert organizations, and the concept of the Quadruple Aim of health care delivery has been widely adopted across institutions [11-13]. The Quadruple Aim was born out of the need to add provider satisfaction and well-being to the initial Institute of Health Improvement's Triple Aim of better health, lower cost, and better care [12].

Apart from the contributions of technology (EHR) to the dissatisfaction of clinicians, the sociocultural and work processes also play an important role in the determination of successful implementation. The interplay of technology and process efficiency described in sociotechnical constructs is very important for overall success [14-18]. In essence, a superb technology application or EHR deployed in an inefficient system will not succeed [19]. Based on this premise, our Beyond-GROSS project will involve soliciting feedback from clinicians about workflow and process issues in addition to EHR-specific problems (see [Figure 1](#) for a diagram of overall project workflow).

Figure 1. Beyond-Getting Rid of Stupid Stuff (GROSS) flow chart.

Beyond-GROSS dovetails with our existing EHR governance structures and other efforts of the Mount Sinai Health System to alleviate the issue of EHR burden through its various EHR optimization workgroups. Apart from the required initial mandatory online EHR training for all new clinicians at Mount Sinai Health System, there are governance mechanisms to increase EHR use proficiency among clinicians and to optimize and standardize the EHR configuration, navigation, and content. These include ambulatory and inpatient EHR optimization working groups, which are collaboratively led by members of the Clinical Informatics Group and Information Technology (IT). The Clinical Informatics Group is a unit reporting to the Chief Medical Information Officer (CMIO). These working groups are comprised of members from many clinical

departments and lead analysts from the EHR applications teams. Clinicians can bring EHR change requests to these bodies through their department's members. The working groups discuss proposed changes, seek additional departmental feedback as needed, and make decisions. Then, the analyst representatives ensure that build changes are made. Mount Sinai Health System also operates an EHR physician champion program whereby the physician champions in each department serve as resource persons for other clinicians who need help using and navigating the EHR. In many cases, these departmental physician champions are also representatives to the EHR working groups.

Our intervention adds the first mechanism through which clinicians can directly report issues via the EHR. It expands request categories and captures more granular aspects of

requests. The intervention expedites fast fixes where possible and appropriate channeling for resolution. The Beyond-GROSS team members, a multidisciplinary subset of the Clinical Informatics Group including the Deputy CMIO, triage reported issues for type of resolution needed (eg, user education, EHR quick fix, potential workflow issue with EHR component); appropriately channel requests outside of the team as needed, including directly to Epic analysts and existing EHR working groups; and guide requests through to resolution.

Methods

Intervention Setting and Population

The program will be implemented in the Mount Sinai Health System, New York City, NY, which is composed of 8 hospital campuses, 13 ambulatory surgical centers, and over 6600 primary and specialty care physicians. We plan to start by conducting a pilot program in a service line of the main campus of the Mount Sinai Hospital and gradually scale the project across the health system over 2 years.

Participants in the pilot will be comprised of clinicians in our academic gastroenterology practice spanning inpatient, outpatient, and endoscopy services, which includes 25 attendings, 14 fellows, and 5 nurses, with a patient volume of more than 6000 endoscopy procedures and 26,800 outpatient visits. This division is an excellent pilot group because it has an engaged workforce comfortable with using technology and a focus on wellness and quality, and it is comprised of a variety

of team members across 3 key settings who are all using the EHR to support care delivery.

Intervention Design and Procedure

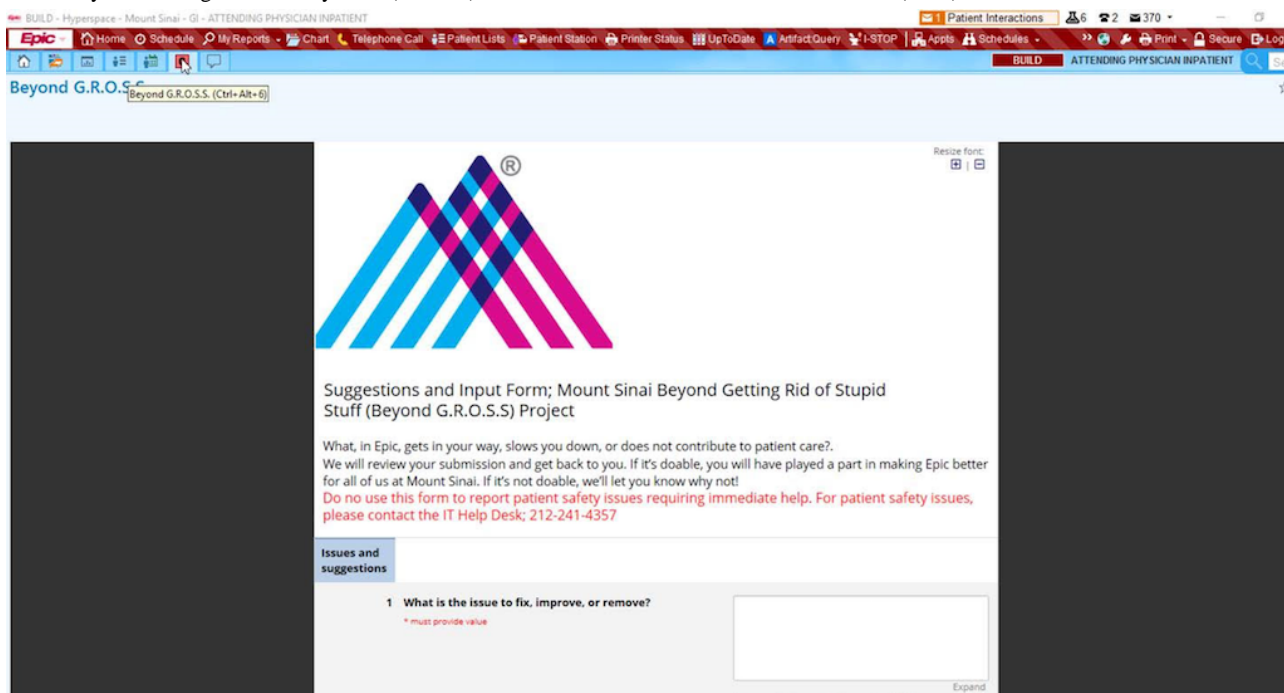
The overall design will be mixed methods utilizing both qualitative and quantitative methods of data gathering and analysis in a Plan-Do-Study-Act (PDSA) iterative approach of quality improvement.

The project will solicit suggestions and input from front-end clinicians (physicians and nurses) about the EHR and workflow issues they encounter during their daily tasks. They will be also encouraged to come forth with suggested ways of overcoming the issues raised. Our initial pilot will take place over a duration of 4-6 months with the intention to implement the program throughout our health system over a period of 2 years. Lessons learned from data analysis and project evaluation will be incorporated in a PDSA fashion every 8 weeks as we scale throughout the organization.

Data Collection Tool, Data Management, and Analysis

We will be soliciting input from clinicians through a form built in the REDCap data capture application with a link to the form conveniently located in the homepage of the EHR for easy access when they encounter documentation that can be optimized (see Figure 2 for Beyond-Gross icon “G” embedded in the EHR) [20]. Clicking the icon opens the form in a browser for data input by the clinician. The G icon was embedded in the EHR (Epic EHR) with the help of an in-house Epic analyst (see Figure 2 for the “G” icon in EHR with link to the REDCap database).

Figure 2. Beyond-Getting Rid of Study Stuff (GROSS) link embedded in the electronic health record (EHR).



The technicalities involve creating a new activity in text located at the top tab. Parameters like link title and URL were set, and filters were placed limiting the activity to only the Gastroenterology Division. The new activity was also added to the desired roles so that only physicians and nurses in the

designated department would see the Beyond-GROSS link “G” in their top tab once they log into Epic.

The data from the form are then automatically stored in our health system’s secure instance of the REDCap database for further analysis by our team. The REDCap form is made up of

2 sections: The first section contains questions relating to the potential issues raised by the frontline clinician and specific issue, location where the issue occurred, and best way to follow up with requesters (see [Textbox 1](#) for form content and description); this corresponds to questions 1 through 11 in the form. The second aspect of the form is for completion by an assigned Beyond-GROSS team member for further analysis of

the requester's input. This section was set up in REDCap to be visible only to an authorized Beyond-GROSS team member for the purpose of analysis; this corresponds to questions 12 through 33 of the survey ([Table 1](#)). A sample of the overall request instrument can be found in [Multimedia Appendices 1-4](#).

Follow-up on input received and analysis of data input include the items listed in [Textbox 2](#).

Textbox 1. The contents of the REDCap form section that will be filled out by a clinician requester.

1. Issues and suggestions:
<ul style="list-style-type: none"> • What is the issue to fix, improve, or remove? • Please upload any supporting document or screenshot. • Why is it beneficial to fix or improve the issue? • Please share any suggestions on how to fix or improve this issue.
2. Contact and location of clinician requester:
<ul style="list-style-type: none"> • What is your name? • What is your email address? • What is the best phone number to contact you? • Where do you work? (hospital/department/clinic) • What EPIC login department did you use when you encountered this issue? • What is your clinical role? (registered nurse [RN], physician, physician assistant [PA], nurse practitioner [NP])

Table 1. The contents of the REDCap form section that will be filled out by a designated Beyond-Getting Rid of Study Stuff (GROSS) team member.

Sections	Specific form questions
Team member	Name of team member handling the issues raised by requester
EHR ^a section concerned	Flowsheet, Smart tools, Orders, BPA ^b , Profiles, etc.
Categorization of issues: nature of the issue	Problem inadvertently created, tools not available, requester unaware of tools, etc.
Categorization of issues: what is required to fix it	Easy fix no build required, requires approval, requester use-optimization needed, not feasible, etc.
Updates	Status of request resolution and communication with users until final resolution and closure

^aEHR: electronic health record.

^bBPA: best practice advisory.

Textbox 2. Process to follow up on requests and communicate with users.

1. An automated email response to the submission received in REDCap will be sent to the requester acknowledging the receipt of the issue noted.
2. Beyond-Getting Rid of Stupid Stuff (GROSS) team members will then proceed with analysis of the request with the intention to categorize the request input for action based on a predetermined categorization scheme (Textbox 1).
3. A personalized email response from one of the Beyond-GROSS team members acknowledging receipt of the REDCap submission and to provide updates on possible solutions to the issue will be sent to the requester within 5 business days.
4. Further clarification may be required from clinician requesters about issues raised in the request via:
 - Email exchanges between the project team members and requester
 - Other basic qualitative methods may be needed for further understanding depending on request type:
 - Personal interview with requester
 - Walk through of affected unit to observe workflow
 - Field study or observation of affected unit
 - Diary studies
 - Focus group
5. Request classification by Beyond-GROSS team members for action and issues or requests will be categorized based on:
 - The nature of the request
 - Requester unaware of extant tools/resources to undertake task efficiently
 - Requester aware of extant tools but not proficient at using tools/resources
 - Tools/resources for task not available
 - Tools/resources exist but improvements are needed to undertake clinician's task efficiently
 - Never meant to occur/inadvertent
 - Workflow/process optimization required; no direct electronic health record (EHR) fix
 - What is required to address/fix issues
 - Easy fix; minimal/no build required; no patient safety consequences if stopped
 - Approval by the hospital's regulatory and patient safety committee needed
 - Newer tools or build needed
 - User optimization or training needed
 - Not feasible to fix
 - Workflow or process reengineering is needed
 - Requires multiple dimensions to fix; both workflow re-engineering plus any other EHR issues (see above)
6. After team categorization of a request, issues will be escalated to the respective stakeholders concerned for resolution of the issue. Such stakeholders include EHR analysts, the safety and regulatory committee, unit leadership, information technology leadership, etc.
7. A follow-up email will be sent to the requester by a designated Beyond-GROSS team member to give an update on the request input within 4 weeks of filling out the request form:
 - Request not feasible and why
 - Feasible and work in process with estimated time to complete
 - Feasible but unable to proceed for now and reason stated
 - Completed and resolved

In the event the issue is not resolved within 4 weeks of filling out the request form, the requester will be given a monthly update of the ongoing work on the issue raised until final resolution is reached.

Data Capture After Query Categorization and Resolution

Apart from assisting with internal audit and quality improvement purposes, we hope to share lessons learned and quality improvement achieved in standard publications and presentations. We will be analyzing both quantitative and possible qualitative data that results from the intervention.

Qualitative Data

Qualitative data will be collected using multiple methods. A postresolution survey will be conducted with requesters to solicit suggestions to improve the project and information on the impact of the project on provider and staff engagement. Iterative transcriptions and data will be obtained from requester interviews or focus group inquiry conducted as part of our PDSA cycles depending on the nature of participants' requests. Iterative transcriptions from any further qualitative activities carried out to understand issues raised (eg, interviews, field observations) will also be recorded. In the event an interview is conducted, the interviews will be transcribed verbatim. The data found in the interviews will be categorized and analyzed using manual thematic analysis [21]. We will also collect data on clinician satisfaction and the impact on engagement.

Quantitative Data

Quantitative data will also be collected using multiple methods, including direct data from our project database and the amount and percentage of requests in each query category, based on the nature of the query and what is required to address issues: percentage of requests directly related to the EHR and percentage of workflow issues not directly related to the EHR.

As applicable and when possible, we will attempt to capture the impact of solution(s) resulting from the Beyond-GROSS project after a predetermined duration of implementation: impact on cost reduction, reduction in errors, reduction in time on the task to figure out baseline before the issue was fixed and repeated after implementation of fixes to determine impact, increase in patient satisfaction where applicable, and other indices as dictated by the specific issue fixed.

Quantitative data will be analyzed using SPSS 20.0 (IBM Corp, Armonk, NY).

Ethics and Governance

The project will be conducted according to the ethical guidelines of the Helsinki declaration [22]. The study is a quality improvement project. The Icahn School of Medicine Institutional Review Board (IRB # 20-04212) determined that it did not need institutional review board review.

Results

We have formed our team, the project charter has been inaugurated, and the CMIO and other IT leaders have approved the project. The leadership approval also grants the Beyond-GROSS team access to utilize our IT service help desk, which we use to engage members of Epic analyst teams and other IT teams as needed to resolve EHR issues. The pilot will run for 4-6 months with formative evaluation and potential

adjustments every 4 weeks. Logistic discussions with the Gastroenterology Division have been completed. Our EHR analysts have embedded the REDCap form link in the home page of the HER, and the project launched in October 2020. Lessons learned from the pilot phase will help us scale to the whole enterprise in phases based on available resources.

The data obtained from the project will provide us with information about aspects of our EHR that hinder efficiency. This information will be useful to our EHR vendor as they plan subsequent upgrades to make improvements. Data will also show us areas in the EHR for which requesters are not using the available tools to efficiently undertake their work. This information will be highly useful to our EHR optimization team because it will assist in determining areas of priority during future training and optimization sessions. Data on time-to-response from the various committees and stakeholders will serve as a means of an internal audit of our informatics governance structure. The direct impact of project on quality will also be sought.

The outcome of most of the issues fixed may not be immediately quantifiable. Also, we are unable to know ab-initio which issues requesters will report, and as such, we are unable to make a specific determination about indices to quantify improvement. However, we hope to incorporate lessons learned from the pilot project to arrive at possible indices for quantifying quality improvement.

We intend to disseminate this information to stakeholders through research or quality improvement forums and peer-reviewed journals.

Discussion

Many clinicians find it undesirable and time consuming to call the IT helpdesk for IT-related or workflow issues encountered during clinical care, mostly due to long wait times when the health system's IT helpdesk is contacted for EHR-specific inquiries [23]. This project will assist in mitigating identified factors that encourage workaround behaviors amongst clinicians, which include perceived or real workflow blocks, and problematic rules that have outlived usefulness, hindering smooth operation; poor workflow design; and other issues [6].

Small tweaks may improve efficiency and reduce burnout in the long run while also improving patient safety. This project may give rise to workflow reengineering, since sociotechnical and process issues also play an important role [19]. The process of getting direct input from staff and clinicians in this project may increase employee engagement, morale, and satisfaction. Most clinicians are delighted to be part of positive force of change, and implementing employee feedback increases sense of belonging and job satisfaction [7,24].

We hope to reap all the benefits of the highest level of health care usability and human-centeredness maturity model as proposed by the Healthcare Information Management System Society and increase individual and organizational efficiency [25].

We will also be using informatics to achieve the desired state of a learning health system as recommended by the National Academy of Medicine as we facilitate feedback loops and rapid cycles of improvement [26].

Although an earlier version of the Beyond-GROSS project achieved high clinician satisfaction in the implementation at

Hawaii Pacific, it is not without its limitations. The inability to identify objective quantitative indices prior to implementation is an identified limitation. Another limitation is that it may be challenging to implement in a center with resource limitations: personnel, database, and IT infrastructure.

Conflicts of Interest

None declared.

Multimedia Appendix 1

BEYOND-GROSS survey instrument Page 1.

[PNG File , 184 KB - [resprot_v10i3e25148_app1.png](#)]

Multimedia Appendix 2

Beyond-GROSS survey instrument page 2.

[PNG File , 221 KB - [resprot_v10i3e25148_app2.png](#)]

Multimedia Appendix 3

Beyond-GROSS survey instrument page 3.

[PNG File , 197 KB - [resprot_v10i3e25148_app3.png](#)]

Multimedia Appendix 4

Beyond-GROSS survey instrument page 4.

[PNG File , 108 KB - [resprot_v10i3e25148_app4.png](#)]

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Abbreviations

CMIO: Chief Medical Information Officer

EHR: electronic health record

GROSS: Getting Rid of Stupid Stuff

IT: information technology

PDSA: Plan-Do-Study-Act

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Protocol

Internet-Based Individualized Cognitive Behavioral Therapy for Shift Work Sleep Disorder Empowered by Well-Being Prediction: Protocol for a Pilot Study

Asami Ito-Masui^{1,2,3*}, MD; Eiji Kawamoto^{1,2,3*}, MD, PhD; Ryota Sakamoto⁴, PhD; Han Yu⁵, ME; Akane Sano⁵, PhD; Eishi Motomura⁶, MD, PhD; Hisashi Tani⁷, MD, PhD; Shoko Sakano⁸, MD; Ryo Esumi^{1,2,3}, MD; Hiroshi Imai^{2,3}, MD, PhD; Motomu Shimaoka¹, MD, PhD

¹Departments of Molecular and Pathobiology and Cell Adhesion Biology, Mie University Graduate School of Medicine, Tsu City, Mie, Japan

²Departments of Emergency and Disaster Medicine, Mie University Graduate School of Medicine, Tsu City, Mie, Japan

³Emergency and Critical Care Center, Mie University Hospital, Tsu City, Mie, Japan

⁴Department of Medical Informatics, Mie University Hospital, Tsu City, Mie, Japan

⁵Department of Electrical and Computer Engineering, Rice University, Houston, TX, United States

⁶Department of Neuropsychiatry, Mie University Graduate School of Medicine, Tsu City, Mie, Japan

⁷Center for Physical and Mental Health, Mie University, Tsu City, Mie, Japan

⁸Mie Prefectural Mental Medical Center, Tsu City, Mie, Japan

* these authors contributed equally

Corresponding Author:

Eiji Kawamoto, MD, PhD

Departments of Molecular and Pathobiology and Cell Adhesion Biology

Mie University Graduate School of Medicine

2-174 Edobashi

Tsu City, Mie, 514-8507

Japan

Phone: 81 59 232 5036

Fax: 81 59 231 5209

Email: a.2.uk@mac.com

Abstract

Background: Shift work sleep disorders (SWSDs) are associated with the high turnover rates of nurses, and are considered a major medical safety issue. However, initial management can be hampered by insufficient awareness. In recent years, it has become possible to visualize, collect, and analyze the work-life balance of health care workers with irregular sleeping and working habits using wearable sensors that can continuously monitor biometric data under real-life settings. In addition, internet-based cognitive behavioral therapy for psychiatric disorders has been shown to be effective. Application of wearable sensors and machine learning may potentially enhance the beneficial effects of internet-based cognitive behavioral therapy.

Objective: In this study, we aim to develop and evaluate the effect of a new internet-based cognitive behavioral therapy for SWSD (iCBTS). This system includes current methods such as medical sleep advice, as well as machine learning well-being prediction to improve the sleep durations of shift workers and prevent declines in their well-being.

Methods: This study consists of two phases: (1) preliminary data collection and machine learning for well-being prediction; (2) intervention and evaluation of iCBTS for SWSD. Shift workers in the intensive care unit at Mie University Hospital will wear a wearable sensor that collects biometric data and answer daily questionnaires regarding their well-being. They will subsequently be provided with an iCBTS app for 4 weeks. Sleep and well-being measurements between baseline and the intervention period will be compared.

Results: Recruitment for phase 1 ended in October 2019. Recruitment for phase 2 has started in October 2020. Preliminary results are expected to be available by summer 2021.

Conclusions: iCBTS empowered with well-being prediction is expected to improve the sleep durations of shift workers, thereby enhancing their overall well-being. Findings of this study will reveal the potential of this system for improving sleep disorders among shift workers.

Trial Registration: UMIN Clinical Trials Registry UMIN000036122 (phase 1), UMIN000040547 (phase 2); <https://tinyurl.com/dkfmjje>, https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000046284

International Registered Report Identifier (IRRID): DERR1-10.2196/24799

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KEYWORDS

shift work sleep disorders; health care workers; wearable sensors; shift work; sleep disorder; medical safety; safety issue; shift workers; sleep; safety; cognitive behavioral therapy; CBT; online intervention; pilot study; machine learning; well-being

Introduction

Shift Work Sleep Disorder and Burnout Syndrome

Long working hours and shortages of human resources among health care workers have increased the turnover rate among their ranks, which has become a major medical safety issue. Shift work sleep disorder (SWSD) is a circadian rhythm disorder presenting with excessive sleepiness or insomnia associated with shift work. The prevalence of SWSD varies among studies; however, evidence shows that more than one in five shift workers experience SWSD [1]. Irregular sleep among shift workers is recognized as a serious problem leading to burnout [2]. Medical workers in the field of emergency medicine and intensive care are at particularly high risk of burnout syndrome due to the high levels of physical and mental stress, along with irregular sleep and work schedules [3]. Early detection and improvement of conditions that may lead to burnout is a major issue worldwide.

Assessment of SWSD includes medical interviews, sleep diaries, and sleep self-reports. Motivation and adherence are central to SWSD management outcomes. Circadian adaptation with the help of bright light and melatonin treatment are part of the clinical treatment for SWSD. Another crucial component of treatment is improving sleep by practicing good sleep hygiene, adjusting sleep conditions, and taking effective naps. Many clinical approaches to SWSD can be considered broadly behavioral [1].

Internet-Based Cognitive Behavioral Therapy and Machine Learning

Cognitive behavioral therapy (CBT) for insomnia (CBTI) is a nonpharmacological treatment option for insomnia. CBTI is a psychological approach for improving sleep by adjusting sleep-related habits and misconceptions regarding sleep, thereby reducing sleep-related problems. The main components of CBTI are sleep diaries, education on sleep hygiene, and counseling by sleep specialists. According to clinical practice guidelines for appropriate use and cessation of sleep medication published by the Japanese Society of Sleep Research [4], CBT is positioned as the second-line therapy when pharmacological treatment is unsuccessful. The guidelines further state current evidence showing that CBT is effective as first-line therapy or as combination therapy. With respect to treatment for SWSD, the Japanese Society of Neurological Therapeutics published treatment guidelines for insomnia, hypersomnia, and circadian rhythm disorder, stating that combination therapy of CBT with other treatments is a highly important option [5].

Studies have shown that smartphone apps and web-based internet-based CBTI are equally effective as face-to-face CBTI treatment [6,7]. Internet-based CBTI has been reported to improve not only sleep but also subjective well-being [8]. As discussed above, the behavioral therapy components for SWSD share some of the same components of CBTI; thus, we consider that similar methods can also be applied to SWSD. Since the research subjects of this study are not SWSD patients but rather healthy shift workers with a high risk of developing SWSD, we hypothesize that early intervention using this method will improve sleep and well-being in this population.

To further enhance the effect of CBT, we will incorporate machine learning-based well-being prediction. The roles of machine learning-based well-being prediction include increasing participants' awareness of their well-being and behavior, and helping them to reflect and change their behavior (eg, sleep) to promote their well-being. If the results from the well-being prediction are shown to physicians, additional roles can include supporting physicians to review participants' historical data (eg, Fitbit and surveys) along with behavioral and physiological changes, make clinical decisions, and provide advice before the conditions deteriorate.

Wearable Sensors and Biometric Big Data

Evaluation and interventions for SWSD have been challenging owing to the lack of an objective measurement of sleep under irregular working conditions. Self-reported sleep hours are known to have low reliability and accuracy. However, the use of wearable sensors, which allow for real-time, continuous monitoring over long periods of time, has made it possible to visualize, collect, and analyze the work-life balance of health care workers experiencing irregular sleep and work conditions. A 7-day study of nurses using wearable sensors found that sleep duration, wake time, and napping correlated with fatigue [9]. In addition, the collection of biometric big data using wearable sensors has facilitated the application of machine learning associated with health care management strategies. Several studies have used these data to predict or detect certain states such as stress using machine learning [10]. Thus, applications of wearable sensors to evaluate sleep and work conditions in shift workers can provide important insights that may lead to improvement in quality of life.

Objective

In this study, we hypothesize that internet-based CBT for SWSD (iCBTS), which implements machine learning-based well-being prediction, can improve the sleep durations of shift workers in both healthy and potential SWSD individuals, thereby preventing any decreases to their well-being. We aim to test

this hypothesis by evaluating the effect of iCBTS on sleep duration and well-being using wearable sensors in a university hospital intensive care unit (ICU).

Methods

Study Overview

This is a prospective interventional pilot study consisting of two phases: (1) preliminary data collection and the development of machine-learning models for well-being prediction, and (2) intervention and evaluation of iCBTS for SWSD. The study will include shift workers (physicians and nurses) working at a university hospital ICU. Participants will be asked to wear a wrist-worn biometric tracker 24 hours a day and answer daily questionnaires about their well-being. After phase 1, sleep and well-being data will be used to build an algorithm for well-being prediction. Phase 2 begins with the baseline period (1 week; data collection only), followed by 4 weeks of the intervention period (data collection+intervention) (see details of the two periods in the following Measurements and Intervention subsections). We will compare sleep duration, well-being, and other variables during the baseline and intervention periods in all participants. The primary outcome of this study will be mean sleep duration at the last week of the intervention.

Inclusion and Exclusion Criteria

Inclusion criteria are as follows: (1) shift workers at the Emergency and Critical Care Center, Mie University Hospital; (2) 8 hours of shift work per shift; (3) Pittsburgh Sleep Questionnaire (PSQI) score ≥ 5 . Written consent to participate in this study will be obtained after sufficient information is provided. Exclusion criteria are as follows: (1) diagnosis of sleep disorders such as sleep apnea, restless leg syndrome, and narcolepsy; (2) diagnosis of psychotic diseases such as depression, panic disorder, and anxiety disorder; (3) use of sleep medications; (4) pregnancy; (5) history of contact dermatitis or other skin diseases with a high risk for skin disorders; (6) patients who are judged by the principal investigator or subphysician to be unsuitable as research subjects.

Measurements

For the collection of biometric data, we will use Fitbit Charge 3. Based on the primary data obtained by the wearable's built-in accelerometer, altitude sensor, and heart rate sensor, this wearable sensor allows for the monitoring and collection of the following biometric information: sleep-related information (start/end time of sleep, minutes awake during sleep, time of

each sleep stage), heart rate, and information on activity (number of steps, calories burned, intensity of exercise). Personal information other than the above (eg, location information, phone numbers) cannot be accessed.

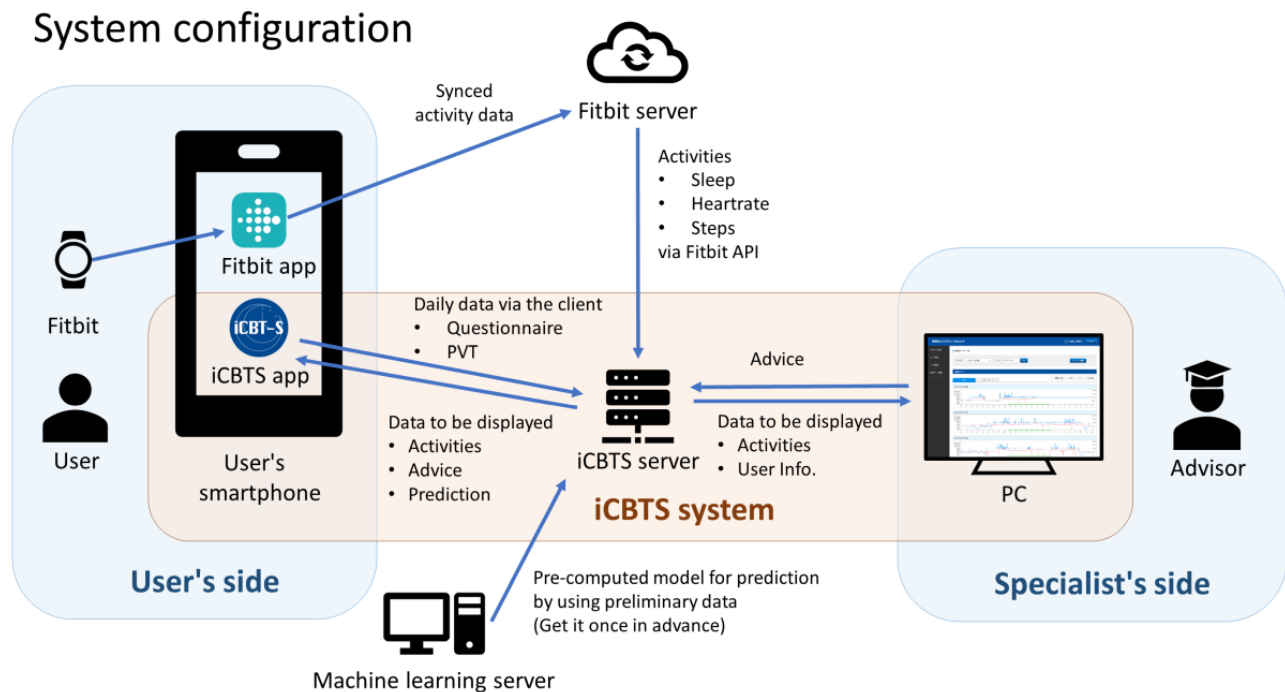
For subjective assessment of well-being, participants will complete morning and evening daily surveys distributed via email or the app. Subjective well-being consists of five categories: alertness, happiness, energy, health, and calmness. The participants will self-evaluate each category with a score ranging from 0 to 100. Other questions in the survey include subjective sleep evaluation (eg, sleepiness, awakenings, satisfaction), and daily activities and habits (eg, events, alcohol and caffeine intake). In addition, as an objective measurement of response to stimuli, participants will take the 3-minute Psychomotor Vigilance Test along with the survey [11]. For evaluation of baseline characteristics and sleep-related conditions, participants will take the following questionnaires before and after intervention: the PSQI, Japanese Epworth Sleepiness Scale (JESS), General Health Questionnaire (GHQ), and State-Trait Anxiety Inventory (STAI).

During the preintervention period, participants are prohibited to access their own activity and sleep data; however, during the intervention period, participants are free to access their own activity and sleep data, and are given personalized sleep advice from physicians 4 times per week (intervention week 1) followed by 3 times per week (intervention weeks 2-4).

Intervention

The smartphone app for the intervention will be developed and available as a Progressive Web Application. No installation is required, and the app can be used on an iOS or Android device. Once the shortcut is placed on the user's home screen, they can immediately access all of the app services. To sign in, participants must enter an ID and password that will be assigned to each individual. The smartphone app is a client of the iCBTS system and is responsible for collecting manual entry information from users, such as questionnaires. The system also provides research coordinators and sleep specialists with a management portal for writing and sending advice to users. The system can further predict well-being based on the model obtained in advance along with daily data collected from Fitbit, and feeds back to the user's app with advice (Figure 1). The dashboard contains three main features: well-being prediction of the day, the surveys that need to be answered, and the shift schedule of the participant.

Figure 1. The internet-based cognitive behavioral therapy for shift work sleep disorder (iCBTS) system uses a smartphone app as a client to obtain questionnaires and other manual entry information from users. The system also provides a management portal for sleep professionals. Advice entered by specialists and predictions based on daily activities from Fitbit are displayed in the user's app.



Well-being prediction is one of the essential components of the app. Based on earlier studies of machine learning and subjective well-being [12,13], we have categorized well-being into five components: alertness, happiness, energy, physical health, and calmness. These prior studies have predicted well-being labels using wearable sensors, mobile phones, and surveys. These studies have used the following metrics to evaluate the well-being prediction performance: accuracy in classification and mean absolute error (MAE) in regression models, calculated as follows:

Accuracy: $\text{Number of true predictions} / (\text{number of true predictions} + \text{number of false predictions})$

MAE: $\text{mean}(|\text{ground truth} - \text{predicted value}|)$

Yu et al [13] used passive mobile phone data (eg, phone calls, SMS text messages, screen usage) and wearable sensor data (electrodermal activity, skin temperature, body accelerometer) from 243 college students to develop a long short-time transfer learning neural network model that could predict the students' next-day well-being status, including subjective happiness, physical health, and calmness, in a 0-100 regression task. The MAE of the regression models were 13.5, 13.2, and 14.4 for happiness, health, and calmness, respectively. Yu et al [14] also leveraged wearable sensor data (eg, heart rate, step count, sleep) and questionnaire responses (eg, work hours, caffeine/alcohol/drug intake) from 14 physicians and nurses. They built a job role-based well-being prediction model for predicting the next days' self-reported alertness, happiness, energy, health, and calmness with model performances of 64%, 79%, 71%, 81%, and 84%, respectively, in high/low binary classification; 59%, 52%, 51%, 58%, and 57%, respectively, in

high/mid/low three-class classification; and 17.4, 15.1, 17.7, 15.4, and 15.6, respectively in regression.

In this study, well-being prediction will be based on these five self-reported labels on a scale of 0 to 100, which are collected twice daily (8 AM and 8 PM). To predict well-being scores, we developed a job-based multitask and multilabel convolutional neural network-based well-being prediction model using pilot data from 14 participants with a total of 241 days of data collection [14]. Twenty-three daily features were extracted from the wearable sensor and daily surveys, including biobehavioral features such as sleep duration, sleep variability, the number of steps, and average and variability of heart rate for the previous 1-7 days; work-related features such as shift schedule and working hours; and daily habits such as alcohol and caffeine intake. The model extracted high-level features using convolutional kernels and predicted five well-being scores simultaneously for physicians and nurses. The prediction performance of the proposed model was compared with that of control models, including job role-based multitask only and multilabel only (doctors only, nurses only, and all participants), and baseline models such as support vector machine and random forest. The proposed model achieved the best performance in almost all of the evaluations performed. In particular, the happiness score, which is considered to be representative of well-being, is illustrated by a graphic that resembles a weather forecast: cloudy for scores 0-50, cloudy and partly sunny for scores 60-80, and sunny for scores 90-100 (Figure 2). The well-being prediction result is updated every morning on the app screen based on the data collected up to the previous evening.

Figure 2. Well-being prediction is displayed in numbers (rounded to the nearest 10) and as a visual icon that resembles a weather forecast: cloudy for scores 0-50, cloudy and partly sunny for scores 60-80, and sunny for scores 90-100.



The app has a total of five tabs: “dashboard,” “activity/sleep chart,” “surveys,” “advice,” and “user profile.” On the “activity/sleep chart” tab, participants will see at a glance how much activity and sleep they have had in 24 hours for the past 7 days. These data are retrieved every hour from the Fitbit server

using its web application programming interface. Awakenings are displayed as red bars, where higher activity levels (higher number of steps per minute) are shown in deeper shades of red, and sleep episodes are displayed as blue bars, where deeper sleep stages are shown in deeper shades of blue (Figure 3).

Figure 3. The app has a total of five tabs: “dashboard,” “activity/sleep chart,” “surveys,” “advice,” and “user profile.” On the “activity/sleep chart” tab, participants will see at a glance how much activity and sleep they have had in 24 hours for the past 7 days.



On the “advice” tab, participants read personalized sleep advice from physicians who specialize in sleep, which are distributed 3 to 4 times a week. The physicians are anonymous to the participants, providing only information on their age, sex, and profession as their profile. Physicians conduct their assessments based on the 23 daily features collected via wearable sensor and surveys. Well-being prediction results are not shown to the physicians; thus, the sleep advice is based solely on clinical judgment of the physicians. Physicians will choose 3-5 messages among 23 fixed-format sleep advice messages (eg, “Avoid alcohol before you go to sleep,” “Try to wake up at a consistent time”). Participants are notified as soon as the sleep advice is written and sent. They are also asked to send their response indicating whether or not they are eager to comply with each piece of advice, in which a thumbs up indicates “eager to follow” and a thumbs down indicates “difficult to follow.” However, the physicians do not further reply to the comments. The aim for this feedback is to ensure that participants read the advice in a timely fashion, and to allow for their interactive participation, thereby potentially enhancing their motivation to continue.

During the baseline data collection period, participants are unable to access most of the features of the app and can only enter the surveys. After day 8 of the study, they will gain access to all of the app features.

Sample Size and Power Calculation

The results of the study performed during phase 1 showed that the mean sleep duration among 16 shift workers was 334.68 (SD 135.1) minutes. The mean sleep duration in the baseline period of phase 2 is assumed to be statistically similar to that assessed in phase 1, as these phases are performed under similar conditions. Based on the pilot study data with a small sample, mean sleep duration at week 4 of the intervention was assumed to be 30 minutes longer, with no change in the SD. Assuming a two-sided level of significance of 5%, power of 80%, and correlation coefficient of 0.8, using the SAS system (SAS Institute Inc, Cary, NC), the number of participants needed for a significant difference to be found in the paired *t* test was calculated to be 66. We set the required number of participants at 70 because the dropout rate of the study was assumed to be about 5% of the enrolled individuals. Dropout rates of

face-to-face CBTI in randomized controlled trials are reported to range from 0% to 8% [15]. According to prior studies, the mean attrition rate of internet-based psychological intervention programs performed in the workplace is 23%, with a range of 3% to 54% [16]. Dropout rates of internet-based sessions tend to be higher than those of face-to-face sessions. However, we estimate that a low dropout rate can be achieved due to the high frequency of feedback from sleep physicians. In addition, a prior study performed in the same ICU targeting health care workers using wearable sensors showed a low dropout rate of 0% [17]. At Mie University Hospital where this study is performed, approximately 75 medical staff members are working in the ICU at any given time, and about 95% of them can be expected to provide consent and participate in the study.

Outcome and Statistical Analysis

The primary outcome of this study is mean sleep duration on week 4 of the intervention. The means and SDs of sleep duration will be calculated at both the baseline data collection period and at week 4 of the intervention period. For the primary endpoint, a two-sided paired *t* test will be performed and assessed at the 5% significance level. In addition, the mean and SD of the changes in sleep duration will be calculated based on the difference between the mean sleep duration of the baseline period and week 4 of the intervention period.

The secondary outcomes of this study are as follows: activity (calories burned, steps taken), subjective well-being, reaction time, and quality and quantity of sleep. Median and quartile values for week 1, week 4, and for the rate of change will be calculated, and the Wilcoxon signed-rank test will be performed at the 5% significance level on both sides. In addition, we will perform a regression analysis of the time-series data (autoregressive model). This analysis will include all data collected during the study period as opposed to other analyses, which will use only data collected at the first and last weeks of the study. The median and quartiles will be calculated for the PSQI, JESS, STAI, and GHQ scores at both pretest and posttest, and the Wilcoxon signed-rank test will be performed at the 5% significance level on both sides. Using the cases in phase 1 as the control group and the cases in phase 2 as the intervention group, the means and SDs of the change in sleep duration will be calculated, and the Student *t* test will be performed at a significance level of 5% on both sides. Additionally, descriptive analysis will be performed to summarize the baseline characteristics of the participants in both groups.

Results

This study was reviewed by The Clinical Research Ethics Review Committee of Mie University Hospital and was approved on January 25, 2019 (phase 1) and May 17, 2020 (phase 2). Both trials are registered with the UMIN Clinical

Trials Registry (phase 1: UMIN000036122, phase 2: UMIN000040547). Data collection in phase 1 was completed in October 2019, with full data obtained from 16 participants. In phase 1, the mean sleep duration was 334.68 (SD 135.1) minutes. As of September 2020, additional results from the trial were still being analyzed and evaluated. After revising and validating the optimal app function, recruitment for phase 2 started in October 2020. This study is expected to be completed by summer 2021.

Discussion

The goal of this study is to explore the efficacy of iCBTS empowered by machine learning well-being prediction to improve the sleep durations and well-being of medical shift workers. Several insights could be derived from this study. First, we expect to clarify the effect of iCBTS for improving sleep and well-being in healthy shift workers, thus indicating internet-based CBT as a potentially effective preventive method for SWSD. Second, we will determine the role of machine learning in CBT. In a broad sense, machine learning in the field of medicine is rapidly expanding, particularly in areas such as risk stratification [18], medical imaging [19], and clinical diagnosis [20]. One of the purposes of CBT is to prompt patients to change the way they think or notice their own misconceptions. We propose that well-being prediction may prompt the user to become more aware of their well-being and behaviors that may influence their well-being, which may in turn promote behavioral change.

The technological limitations of this study are the sensing accuracy of the wearable sensor, which can be mediated by several factors under real-life settings. Even though several validation studies have already compared wearable sensor technology to conventional monitoring methods, and have indeed showed promising results [21], no scientific consensus has been reached to date. A second limitation is the difficulty of tracking subjective well-being, which can likely vary considerably throughout the day. Although increasing the number of sampling self-reported surveys may alleviate this problem, we believe that a higher frequency of self-reported well-being sampling to be challenging for busy shift workers. Another potential limitation is the accuracy of well-being prediction, which is difficult to validate. Moreover, this study cannot determine whether iCBTS is effective above mere participation in the study.

Future goals of this study include improvement and adjustment of well-being prediction algorithms, and strategies for the effective use of this iCBTS method to better support medical managers and physicians. In addition, further research is needed to examine the results in different organizational settings with shift workers.

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Authors' Contributions

AM, EK, and MS designed and supervised the project; AM, HY, and AS wrote the manuscript; RS created the figures; RE, EM, HT, SS, and HI contributed to design of the protocol and edited the manuscript. MS and AS edited and finalized the manuscript. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

AS has received travel reimbursement or honorarium payments from Gordon Research Conferences, POLA Chemical Industries, Leuven Mindgate, American Epilepsy Society, and IEEE. AS has received research support from Microsoft, Sony Corporation, NEC Corporation, and POLA Chemicals, and consulting fees from Gideon Health and Suntory Global Innovation Center. AS was paid by the European Science Foundation for a grant review. All other authors have no conflicts to declare.

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Abbreviations

CBT: cognitive behavioral therapy

CBTI: cognitive behavioral therapy for insomnia

GHQ: General Health Questionnaire

iCBTS: internet-based cognitive behavioral therapy for shift work sleep disorder

ICU: intensive care unit

JESS: Japanese Epworth Sleepiness Scale

MAE: mean absolute error

PSQI: Pittsburgh Sleep Questionnaire

STAI: State-Trait Anxiety Inventory

SWSD: shift work sleep disorder

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Protocol

Remote and Long-Term Self-Monitoring of Electroencephalographic and Noninvasive Measurable Variables at Home in Patients With Epilepsy (EEG@HOME): Protocol for an Observational Study

Andrea Biondi¹, MSc; Petroula Laiou¹, PhD; Elisa Bruno¹, MD, PhD; Pedro F Viana^{1,2}, MSc, MD; Martijn Schreuder³, PhD; William Hart⁴, PhD; Ewan Nurse^{4,5}, PhD; Deb K Pal¹, PhD; Mark P Richardson¹, BMBCh, PhD

¹Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom

²Faculty of Medicine, University of Lisbon, Hospital de Santa Maria, Lisbon, Portugal

³ANT Neuro UK, Ltd, Stevenage, United Kingdom

⁴Seer Medical Inc, Melbourne, Australia

⁵Department of Medicine, St. Vincent's Hospital Melbourne, The University of Melbourne, Melbourne, Australia

Corresponding Author:

Andrea Biondi, MSc

Institute of Psychiatry, Psychology & Neuroscience

King's College London

5 Cutcombe Rd

London, SE5 9RT

United Kingdom

Phone: 44 7753986485

Email: andrea.2.biondi@kcl.ac.uk

Abstract

Background: Epileptic seizures are spontaneous events that severely affect the lives of patients due to their recurrence and unpredictability. The integration of new wearable and mobile technologies to collect electroencephalographic (EEG) and extracerebral signals in a portable system might be the solution to prospectively identify times of seizure occurrence or propensity. The performances of several seizure detection devices have been assessed by validated studies, and patient perspectives on wearables have been explored to better match their needs. Despite this, there is a major gap in the literature on long-term, real-life acceptability and performance of mobile technology essential to managing chronic disorders such as epilepsy.

Objective: EEG@HOME is an observational, nonrandomized, noninterventional study that aims to develop a new feasible procedure that allows people with epilepsy to independently, continuously, and safely acquire noninvasive variables at home. The data collected will be analyzed to develop a general model to predict periods of increased seizure risk.

Methods: A total of 12 adults with a diagnosis of pharmaco-resistant epilepsy and at least 20 seizures per year will be recruited at King's College Hospital, London. Participants will be asked to self-apply an easy and portable EEG recording system (ANT Neuro) to record scalp EEG at home twice daily. From each serial EEG recording, brain network ictogenicity (BNI), a new biomarker of the propensity of the brain to develop seizures, will be extracted. A noninvasive wrist-worn device (Fitbit Charge 3; Fitbit Inc) will be used to collect non-EEG biosignals (heart rate, sleep quality index, and steps), and a smartphone app (Seer app; Seer Medical) will be used to collect data related to seizure occurrence, medication taken, sleep quality, stress, and mood. All data will be collected continuously for 6 months. Standardized questionnaires (the Post-Study System Usability Questionnaire and System Usability Scale) will be completed to assess the acceptability and feasibility of the procedure. BNI, continuous wrist-worn sensor biosignals, and electronic survey data will be correlated with seizure occurrence as reported in the diary to investigate their potential values as biomarkers of seizure risk.

Results: The EEG@HOME project received funding from Epilepsy Research UK in 2018 and was approved by the Bromley Research Ethics Committee in March 2020. The first participants were enrolled in October 2020, and we expect to publish the first results by the end of 2022.

Conclusions: With the EEG@HOME study, we aim to take advantage of new advances in remote monitoring technology, including self-applied EEG, to investigate the feasibility of long-term disease self-monitoring. Further, we hope our study will

bring new insights into noninvasively collected personalized risk factors of seizure occurrence and seizure propensity that may help to mitigate one of the most difficult aspects of refractory epilepsy: the unpredictability of seizure occurrence.

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KEYWORDS

epilepsy; EEG; electroencephalography; brain ictogenicity; wearables; seizure prediction; brain; seizures; mobile technology

Introduction

Background and Rational

Epilepsy is one of the most common neurological disorders, affecting over 65 million people worldwide, and is characterized by recurrent seizures [1]. The unpredictability of these events is one of the key challenges in this disorder. One in 3 people with a diagnosis of epilepsy do not respond fully to antiepileptic drugs and continue to have seizures [2]. Currently, a solution to assess daily seizure risk and understand seizure triggers would be fundamental to improving quality of life and safety for people with epilepsy and allow the testing of new targeted therapies during periods of high seizure risk (chronotherapy) [3] and a better understanding of individual seizure cycles [4,5]. It might prevent accidents and injuries by giving people with epilepsy time to find a safe place before seizure onset [6] and reduce anxiety and stress, which affect 30% to 50% of people with epilepsy [7,8]. Unfortunately, a feasible solution to continuously monitor and assess this risk is not available.

The development of new wearable devices and smartphone apps that could help people with epilepsy to monitor the evolution of their epilepsy would be a clear step in this direction. During the last few years, smartphone apps and wearable devices that allow long-term monitoring of relevant parameters have been developed with the aim to satisfy both the increasingly urgent need for new reliable devices and techniques as well as patient needs and expectations [9].

Smartphone apps now allow people with epilepsy to collect and share with medical professionals information regarding medication, seizure types, and other information that may relate to seizure occurrence [10]. A few studies have used self-reported questionnaires and electronic diaries to explore the association between sleep-wake cycles, menstrual cycles, stress, poor sleep, failure to take treatment, and an elevated seizure risk, revealing a clear relation between some of these variables and seizure occurrence [11-13]. Karoly and colleagues [4] showed that it is possible to identify, using self-reported e-diaries, a subset of patients with robust circadian and multidien seizure cycles. They also reported that estimates of seizure likelihood based on patient-reported cycles were predictive of electrographic seizures [5].

Additionally, some studies have explored the use of wearable devices combining multiple physiological variables to develop automated seizure detection systems [14]. These studies have shown, with different levels of accuracy and sensitivity, that it is possible to detect specific seizure types characterized by stereotyped events (ie, bilateral tonic-clonic seizure) using electrodermal activity, muscle activity, or heart rate [15-18].

Finally, there is strong evidence that factors associated with elevated seizure risk can be objectively detected using electroencephalography (EEG). Video EEG monitoring is the gold standard for the diagnosis of epilepsy. However, conventional video EEG requires patients to stay in the monitoring unit until the collection of multiple seizures is completed. This is an expensive solution and impractical for long-term recording, and it is not well accepted by some patients [19]. Another solution is home video electroencephalographic telemetry. It reduces high costs and long waiting times for hospital admission but presents problems related to long-term electrode attachment on the scalp and correct camera placement while the patient is unsupervised at home, and there are concerns related to regulations regarding data privacy for cloud services [20].

New portable or implantable EEG devices allow for the continuous collection of high-quality data outside of the hospital without direct supervision by a specialist [21,22]. One clinical trial demonstrated a proof-of-principle, real-time seizure prediction system in a cohort of 15 people with epilepsy using an intracranially implanted EEG device (NeuroVista seizure advisory system) [23]. Weisdorf et al [24] and Gangstad et al [25] demonstrated the acceptability and data quality of an implanted subcutaneous EEG system (Uneeeg 24/7 EEG SubQ; Uneeeg Medical) during a long-term trial in outpatients with focal epilepsy. Askamp and Van Putten [26] also showed that the use of a portable EEG solution for at-home assessment (Mobita 32-Channel Wireless EEG System; Twente Medical Systems International) was well accepted by adult patients with intractable epilepsy as well as neurologists and that data collected were comparable with a normal ambulatory scalp EEG. Finally, an ongoing study called HOMEone aims to provide evidence of the diagnostic and therapeutic yield of a patient-controlled portable EEG device (Fourier One; Nielsen Consumer Neuroscience) with dry electrodes for the purposes of EEG home monitoring of neurological outpatients [27]. All these studies [13,23] have shown that it may be feasible and clinically valuable to monitor patients with epilepsy outside of the hospital or research settings thanks to the development of new portable and easy-to-use devices. Despite this, clear information about the long-term and remote acceptability and performance of mobile technology is still not available in the literature.

To bridge this gap, high data quality and good compliance are needed. The first step is the design of an acceptable and feasible procedure to noninvasively monitor patients at home. Starting from this key point, we decided to design a procedure (EEG@HOME) to investigate whether frequent measurements performed independently by people with epilepsy using a

portable EEG cap with dry electrodes (waveguard touch; ANT Neuro), smartphone app (Seer app; Seer Medical), and wrist-worn device (Fitbit Charge 3; Fitbit Inc) in their home environment would be feasible and acceptable.

The successful implementation of an at-home, long-term monitoring procedure like this will enable a novel and innovative approach to epilepsy management. It promises to provide key information to prospectively identify periods of higher seizure risk and improve the management of epilepsy.

Study Objectives

The main goal of the EEG@HOME study is to develop and test a feasible and acceptable procedure for people with epilepsy to easily undertake twice-daily, at-home EEG coupled with an event app and continuous data collection from a wrist-worn wearable sensor device. All the information gathered about acceptability and feasibility of the procedure will be published and used to refine methods for future and larger controlled studies at home.

The study will produce a substantial amount of continuous data from people with epilepsy over many months. Assuming complete data collection, we estimate having 60 hours of raw EEG data and 4000 hours of raw wrist-worn sensor data collected at home per participant in addition to patient-reported events. Recognizing the uniqueness of the data set, we will curate it and make anonymized data and clinical metadata available to other researchers, with the aim to create an open database for future research.

The unique set of wearable EEG data, sensor data, and self-reported events will be then analyzed to develop a general model to predict periods of increased seizure risk. The association between self-reported events (seizures, medication taking), sensor data (sleep, heart rate), and EEG features will be investigated within and between subjects.

Methods

Study Design and Population

EEG@HOME is an observational nonrandomized and noninterventive study. A total of 12 people with epilepsy referred as part of their routine clinical care to the epilepsy clinics at King's College Hospital and partner hospitals will be enrolled. Patients will be included if they have received a diagnosis of treatment-resistant epilepsy, their age is between 18 and 75 years, and they experience more than 12 seizures (with impaired awareness) per year according to their seizure diary. A current diagnosis of psychogenic nonepileptic attacks (dissociative seizures), inability to comply with the trial procedure or give informed consent, and the use of other

electronic medical devices that could interfere with the data collection will result in exclusion from the study.

Study Overview

Participants will be initially identified among those attending a routine outpatient appointment, hospital video EEG Epilepsy Monitoring Unit admission, or home video EEG monitoring appointment at the participating sites. These individuals will be approached by a member of the on-site research team and given the study participant information sheet. This will be labelled "first approach."

After the participants have at least 24 hours to read the participant information sheet and consider enrolling, the research team will contact the participants and invite them to attend visit 1 (inclusion and training). All study procedures and eligibility criteria will be discussed, and the EEG device and wrist-worn sensor will be shown to the patients. If the patient is willing to participate, written informed consent to participate in the study will be obtained. Procedures for using the equipment will then be explained. By the end of the inclusion and training visit, the participant should be able to collect their own EEG data, wrist-worn sensor data, and app data independently. An appointment for the next visit will be scheduled after approximately one month. The participant will start to collect their data immediately after visit 1.

After this, the patient will attend monthly follow-up visits up to 6 times (visits 2-7), carried out in the patient's home or in the research facility of the hospital, according to participant preference. These meetings will allow the research team to confirm the correct collection and download of the event diaries and sensor data. Furthermore, compliance with procedures will be assessed.

At visit 7, the final study visit, acceptability and usability of the technology will be assessed. Participants will be asked to complete a short questionnaire and then a semistructured interview (15 minutes). The detailed flowchart of all the events is presented in [Figure 1](#).

This study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964); The Research Governance Framework for Health and Social Care (second edition, 2005); the Data Protection Act (2018), which includes the provisions of the General Data Protection Regulation; and the principles of Good Clinical Practice (GCP). All devices are Conformité Européenne (CE) marked for the purpose for which they will be used in this study. All investigators will have up-to-date training in GCP. All staff working on the study have received training in study conduct, informed consent, and risk assessment.

Figure 1. Schedule of events in the EEG@HOME study. BIPQ: Brief Illness Perception Questionnaire; EEG: electroencephalography; PSSUQ: Post-Study System Usability Questionnaire; SUS: System Usability Questionnaires.

Month	0	0	1	2	3	4	5	6
Visit	First approach	1 (Inclusion & training)	2 (Follow-up)	3 (Follow-up)	4 (Follow-up)	5 (Follow-up)	6 (Follow-up)	7 (End)
Study explanation	✓	—	—	—	—	—	—	—
Participant information sheet	✓	—	—	—	—	—	—	—
Informed consent	—	✓	—	—	—	—	—	—
Training	—	✓	—	—	—	—	—	—
Sociodemographics	—	✓	—	—	—	—	—	—
Medical history	—	✓	—	—	—	—	—	—
Monitoring telephone call	—	—	✓	✓	✓	✓	✓	✓
Qualitative interview	—	—	—	—	—	—	—	✓
BIPQ	—	✓	—	—	—	—	—	—
SUS	—	—	✓	✓	✓	✓	✓	—
PSSUQ	—	—	—	—	—	—	—	✓
ANT Neuro EEG	—	Twice per day						
Fitbit Charge 3	—	Continuously						
Seizure diary	—	Every time participant has a seizure						
Medication	—	Every day						
Stress & mood	—	Twice per day						
Sleep quality	—	Every day						

Study Withdrawal

Participants will be free to withdraw from the study at any time. In the case of participant self-withdrawal, a face-to-face appointment will be scheduled to establish the cause of withdrawal, collect qualitative and quantitative data regarding their experience, and collect the EEG system and equipment. All data, including those from study withdrawals, will be included in the final analysis.

Study Technology

The ANT Neuro eego mini-series (miniaturized EEG recording system) and ANT Neuro waveguard touch (easy-to-use 8-channel dry EEG cap) will be used to record EEG twice daily for 10 minutes [28] (Figure 2). These will provide a quick and easy setup that people with epilepsy can use at home without technical support. The dedicated computer recording software

(eego; ANT Neuro) allows the review of the data online and offline and the possibility to parse the data into the standard file format.

The ANT Neuro eego was selected from a shortlist of commercial devices. Following Pinho and colleagues' work [29], an EEG system used for clinical purposes in outpatients must meet 9 requirements: wireless connectivity, dry electrodes, signal resolution, sampling frequency, comfort, portability, signal artifact attenuation, event detection, and event prediction. Neumann et al [27] also added the necessity of an integrated and structured reporting system and full coverage of the 10-20 System of electrode placement. The ANT Neuro eego meets several of these technical demands required for a clinical outpatient EEG system but not all of them. Technical specifications of the device compared with other available devices are also summarized in Table 1.

Figure 2. The ANT Neuro eego mini-series and ANT Neuro waveguard touch.



Table 1. Specifications of commercially available EEG portable solutions for diagnostic or research purposes.

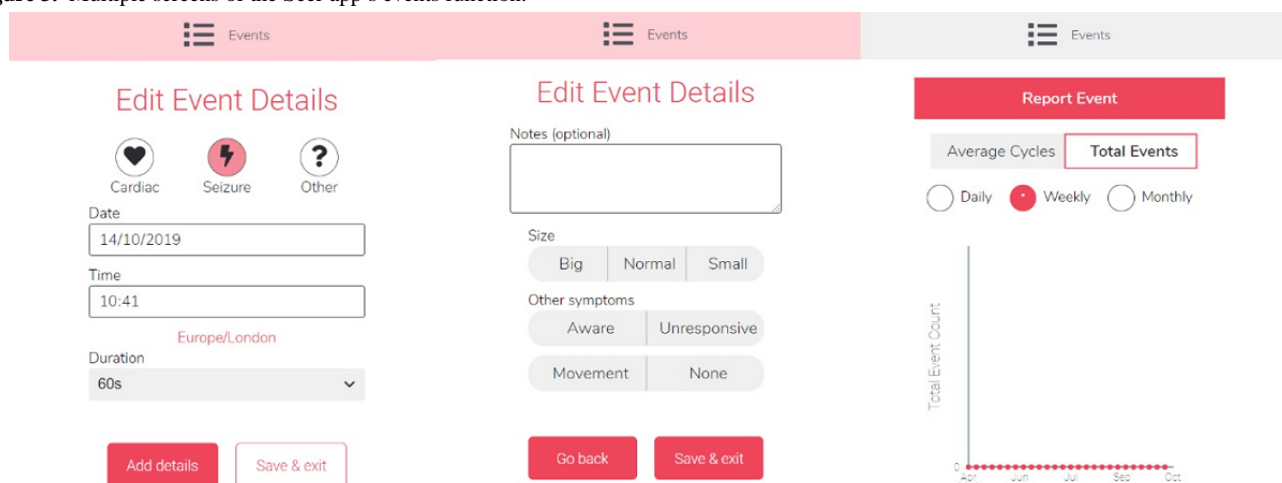
Device (Manufacturer)	Channels	Sample rate	Battery	Resolution	Electrodes	Electrode placement	Weight (g)
Mobita (Twente Medical Systems International)	Up to 32	Up to 2000 Hz	Rechargeable	24-bit	Water-based electrodes	10-20 System	225
Epoc+ (Emotiv)	14	Up to 64 Hz	Rechargeable	16-bit	Saline-based electrodes	10-20 System	170
Fourier One (Nielsed)	19	Up to 500 Hz	Rechargeable	24-bit	Dry silver electrodes	10-20 System	— ^a
Safiro (Compumedics)	32	Up to 512 Hz	Rechargeable	16-bit	Actively shielded electrode wires	10-20 System	270
Enobio (Neuroelectric)	8 to 32	Up to 125 Hz	Rechargeable	24-bit	Handy gel, solid gel, and dry electrode solutions (Ag-AgCl coating)	10-20 System	—
Quick (Cognionics)	8 to 30	Up to 1000 Hz	Rechargeable	24-bit	Dry electrodes (Ag-Ag-Cl coating)	10-20 System	596
Eego amplifier series (ANT Neuro)	8 to 64	Up to 2084 Hz	Connected with a computer or tablet	24-bit	Dry silver electrodes	10-20 System	100

^aNot available.

A Fitbit Charge 3 will be provided, and during the first approach visit, the need to wear the device continuously will be explained. The Fitbit Charge 3 is a consumer-oriented fitness tracker that provides 24/7 estimates of heart rate, estimates of sleep stages, and activity information (steps, calories, sport activity). The device uses a combination of a microelectronic triaxial accelerometer to capture body motion in 3D space and a photoplethysmogram to extract heart rate. Proprietary algorithms are implemented to identify daily steps taken, sleep, and other activities (eg, running, biking) [30]. This device was selected from a list of wrist-worn devices based on dependability,

durability (battery life of up to 7 days), and user acceptability [31]. The Fitbit smartphone app will be installed on the patient's mobile phone through an anonymized email account.

The Seer app (available for Android and iOS devices) [32] is a smartphone app for people with epilepsy to keep track of their seizures and medications. It was created with the aim of helping people with epilepsy manage their symptoms and treatment. It allows patients to report different events, add notes, and receive feedback and visualize it (Figure 3). The Seer app will be downloaded to the patient's mobile phone using an anonymized email account.

Figure 3. Multiple screens of the Seer app's events function.

Data Measured

Electroencephalographic data will be collected using the ANT Neuro eego (approximately 10 minutes of recording while the participant is resting with eyes closed every morning and evening at an interval of approximately 12 hours). First, 1 trained neurologist will visually examine each 10 minutes of EEG recorded, and all the focal interictal epileptiform discharges

(IEDs), generalized spike-wave discharges, and focal slowing will be marked. Then, at least one 20-second segment of EEG while the participant is awake with eyes closed that is free of movement and artifacts, signs of drowsiness or sleep, or IEDs will be selected from each recording.

From each segment, different EEG features will be extracted, starting from simple conventional measures to more complex

and novel biomarkers. Initially, the power spectra will be calculated. Specifically, our analysis will be focused on 5 frequency bands (1-5 Hz, 6-9 Hz, 10-11 Hz, 12-19 Hz, and 21-70 Hz) defined from previous literature [33,34].

The first measure that will be calculated is the alpha power shift. It is defined as the ratio of average power in the low-alpha power (6-9 Hz) over average power in the high-alpha power (10-11 Hz). Abela and colleagues [35] compared patients with good and poor (4 or more seizures in 12 months) seizure control, showing that alpha power shift is a robust indicator of seizure liability.

In addition, from each 20-second EEG segment, we will infer functional brain networks in which each node corresponds to the brain region underneath each electrode and the edges denote statistical dependencies between the corresponding EEG signals. We will use the phase-locking factor, ignoring all connections at zero lag [36] as well as those that are not statistically significantly different from surrogate data [37]. We will quantify structural properties of the functional brain networks using graph theory metrics, such as the mean and variability of the degree distribution and clustering coefficient [33,38].

Complementary to this graph theory analysis, we will employ a computational modeling framework, the so-called brain network ictogenicity (BNI), which quantifies the propensity of a brain network to generate seizures [39,40]. In this modeling framework, brain models that are able to transit between normal and seizure-like activity are connected using the same connectivity obtained from the functional network that was computed from the EEG signals. This framework is specific to the individual, since it uses the connections obtained from each individual. In order to quantify the contribution of a single brain region (ie, single node in the functional network) to the generation of seizures, we will use the quantity of node ictogenicity (NI), which measures the changes in BNI upon removal of a single node [40]. Therefore, for each 20-second EEG segment, we will obtain 1 BNI value as well as 8 NI values for each node.

In this study, the mentioned EEG features will be evaluated for their predictive value for seizure occurrence and for their potential association with other variables, like treatment, heart rate, sleep, and mood or stress.

Heart rate will be continuously (24/7) estimated using the Fitbit Charge 3 for 6 months. We will specifically use the output of the Fitbit proprietary algorithm, which estimates heart rate from the photoplethysmography sensors approximately every 5 to 15 seconds. Changes in heart rate that could associate with and potentially predict seizure occurrences will be evaluated [41].

Sleep will be also assessed every day. The Fitbit Charge 3 will provide sleep duration (hours and minutes), sleep stages (hours and minutes spent in deep sleep, light sleep, rapid eye movement, and awake), and a Fitbit Quality Sleep Score Index (from 0 [worst] to 100 [best]). Similar to the heart rate analysis, we will investigate changes in sleep that could associate with and potentially predict seizure occurrences.

Through the Seer app, participants will provide a range of patient-reported outcomes with information regarding their

mood (twice per day, range of 1-5), stress level (twice per day, range of 1-3), sleep quality (in which participants rate last night's sleep compared with the previous night, with choices for worse, usual, and better), medication compliance (twice per day, binary yes or no), and seizure events (seizure start, end, and movement) via brief app questionnaires. The questions were selected and adapted to our study from already published studies focused on seizure precipitants and triggers [11,12]. Changes in these patient-reported outcomes that could associate with and potentially predict seizure occurrences will be evaluated.

To provide information about patient characteristics that could determine compliance and feasibility, a set of questionnaires will be administered. Beliefs and attitudes will be assessed using the Brief Illness Perception Questionnaire (BIPQ). It is a validated 9-item scale designed to rapidly assess the patients' emotional and cognitive illness representations. The questionnaire is structured in 6 sections to assess different factors: consequences (BIPQ 1), timeline (BIPQ 2), personal control (BIPQ 3), treatment control (BIPQ 4), identity (BIPQ 5), concern (BIPQ 6), and emotions (BIPQ 8). Finally, 1 item assesses illness comprehensibility (BIPQ 7) [42].

Two validated questionnaires (System Usability Scale [SUS] and Post-Study System Usability Questionnaire [PSSUQ]) will be used to assess participants' first impressions after the training and the overall experience of the study, respectively. The SUS is a 10-item usability questionnaire that will be used in this study to evaluate interaction with the ANT Neuro EEG recording system and the Fitbit Charge 3. It is an easy and fast scale to administer and has been validated on small sample sizes with reliable results that allow effective differentiation between usable and unusable systems [43].

The PSSUQ is a short and validated questionnaire that will be used in this study to assess patients' experiences with the EEG system and the Fitbit Charge 3. It includes 16 items created to measure users' perceived satisfaction with a system at the end of a study [44].

Finally, a semistructured interview will be scheduled at the end of the study. The researcher will collect direct feedback from the participants about their experience, impression of the devices, comfort, problems and issues, future solutions and improvements, suggestions, reasons for discontinuing wearing a device (if they dropped out), possible concerns, and data privacy and security.

Data Security and Privacy

Each participant will be assigned a sequential identification code (ie, EEGatHOME00?) used to collect, store, and report participant information. The key to the pseudonymization code will be held in the hospital computer system. Each participant will also receive a nonidentifiable email (ie, eeghome001@xxxx.com) that will be used only for data collection and streaming from the apps to the server. All digital and nondigital information related to study participants will be nonidentifiable in accordance with the General Data Protection Regulation.

Data acquired from the ANT EEG system and Fitbit wrist-worn biosensor will be encrypted, pseudonymized, and uploaded

automatically to secure servers managed by the research team and already approved for long-term patient data collection. Data collected from the smartphone app will be also collected and entered in a password-protected database and stored locally and on a secure server. No personally identifying data will be stored or processed within research infrastructure. The research team will assess on a weekly basis the amount of data collected by each participant to evaluate the missing rate and ensure the best data quality.

Clinical information and questionnaires will be collected using pseudonymized forms. Study documents will not contain any identifying information, only study numbers. All questionnaires and documents collected as part of the study process will be stored on password-protected computers.

Although we have access to sufficient infrastructure and storage for the data set for this study, a larger study or real-life rollout of a monitoring system of this kind would require a very large, secure infrastructure that would need to be compatible with legal requirements in multiple countries. These considerations are outside the scope of this study.

Analysis Plan

At the end of the 6 months, for each participant, the research team expects to have up to 4380 hours of continuous data from the Fitbit Charge 3, 365 EEG segments, 730 daily questionnaires, 7 acceptability questionnaires (BIPQ, SUS, and PSSUQ) and 1 semistructured interview. We also expect that during the study, each participant will have at least 6 seizures, and therefore, the total number of seizures across all patients is expected to be at least 72.

Initially, descriptive statistics will be applied on questionnaires (BIPQ, SUS, and PSSUQ) and demographic information (age, sex, and education) to have an overview of the overall experience. Data missing rate will be also calculated for each device and descriptive analysis will be applied. Using regression analysis, we will investigate if any demographics or other numerical information (sleep, mood, stress) serves as a predictor for participant dropout (if it occurs before the end of the 6 months). We will then estimate for each participant whether there is any relationship between the data missing rate and the self-reported measures (sleep, mood, stress) as well as the monthly acceptability assessment (PSSUQ).

Finally, a thematic analysis will be performed on the recorded semistructured interviews and the weekly call. Audiorecordings will be transcribed, and then a thematic analysis will be performed using NVivo software (version 12; QSR International) by 2 researchers working independently. Initially, the major themes and subthemes will be identified. Once all themes and subthemes are labeled, a secondary analysis will be performed to categorize the dimensions extracted.

The quantitative measures will be computed using data from 3 periods: preictal (within a defined period prior to seizures), postictal (within a defined period following seizures), and interictal (all other times). We will rerun our analysis using 3 different time periods for preictal and postictal periods (24 hours, 72 hours, 7 days); interictal time periods of the same duration as the preictal and postictal periods will be randomly

selected from interictal periods approximately equidistant from consecutive seizures. For each peri-ictal period, we will calculate the median of each of the following variables: BNI, variability of NI distribution, mean degree, clustering coefficient, and alpha power shift. We will also calculate the median heart rate, total steps, total sleep hours, mean mood, and mean stress in the 12 hours prior to the EEG measurements.

The primary analysis will be assessed by the area under the receiver operating characteristic curve (AUC) using each of the 5 variables. AUC is the current gold standard for the evaluation of seizure detection and seizure prediction performance.

In an exploratory factor analysis, we will investigate relationships between variables and their independent predictive values using mixed-effects logistic regression models with repeated measurements. For each seizure, the repeated measurements will be the same variables as the primary analysis and the questionnaires (mood, stress, sleep quality, self-assessment of seizure risk, and medication taken) in the preictal, postictal, and interictal periods.

Results

The EEG@HOME project received funding in 2018 by Epilepsy Research UK ([Multimedia Appendix 1](#)) and was approved by the Bromley Research Ethics Committee (REC reference: 19/LO/0554) in March 2020. Pilot data to test the feasibility and practicality of the procedure, from the use of wearable devices to the data analysis, were collected from April to June 2020. The first group of participants were enrolled in October 2020, and the first results are planned to be published by the end of 2022.

Discussion

Study Contributions and Implications

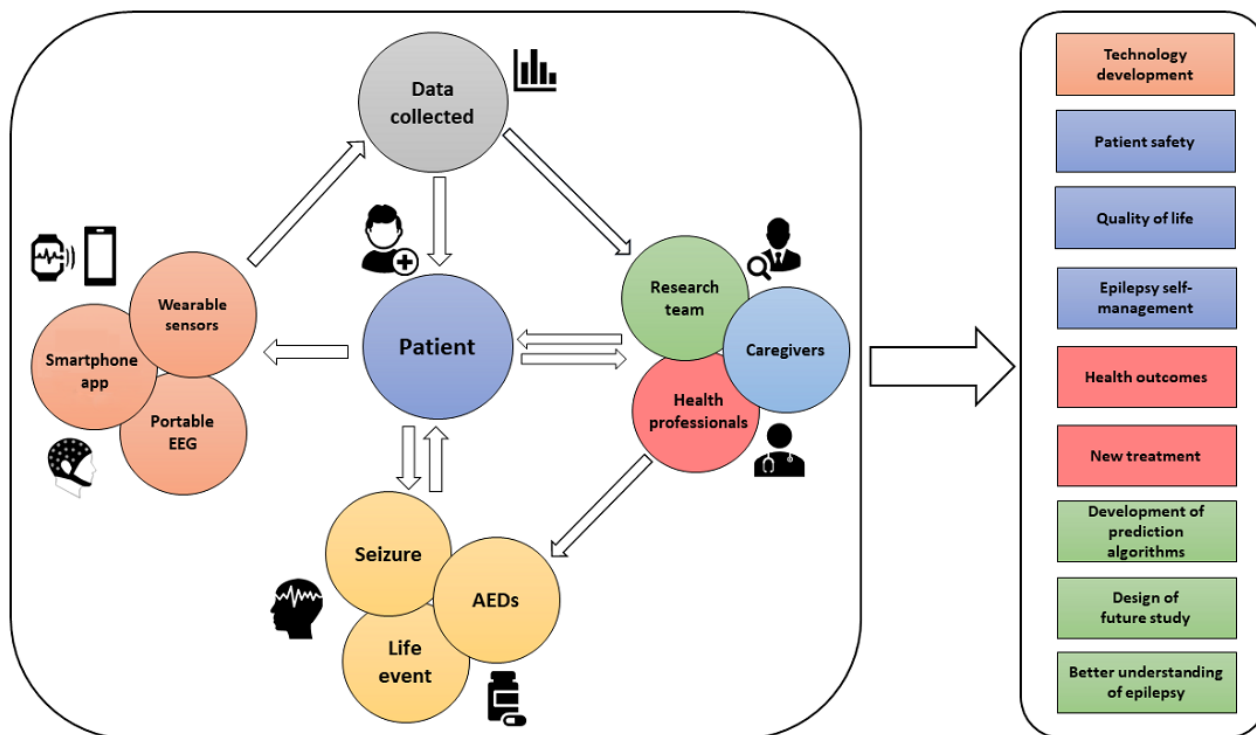
EEG@HOME aims to provide an innovative and flexible procedure that, combining the use of new and multiple technologies, will give patients with epilepsy a solution to monitor their condition independently.

Over 72% of the population in the United States has a smartphone [45], and 60% of people with a mobile phone have downloaded a health app [46]. A recent study also supports the acceptability of new solutions for people with epilepsy, reporting that 80% were willing to use a wearable device for seizure tracking and 69% were also willing to use a smartphone app [47]. These studies highlight the fact that clinical populations are ready to use new technology to better manage their condition. Collecting physiological signals in real time by using a wearable device and self-reporting events with an e-diary can improve compliance and accuracy of epilepsy monitoring [48]. Despite this, a reliable procedure to easily monitor seizure occurrence and triggers that clinicians can recommend to people with epilepsy after initial diagnosis is not currently available. Furthermore, the long-term performance of wearable devices for people with epilepsy has been assessed in only a few studies [23,49].

To better understand the real impact that these new technologies will have in monitoring people with epilepsy in their daily lives as well as the utility of the data collected, more long-term studies in clinical populations are needed. In Figure 4, we propose a model that outlines the possible outcomes that a prolonged

(active and passive) interaction between patients, caregivers, health professionals, and new technology could have in patients' lives, clinical pathways, and research, as we propose in EEG@HOME.

Figure 4. eHealth model of new technology for patients with epilepsy. AED: antiepileptic drug; EEG: electroencephalogram.



One of the main innovations in EEG@HOME will be the use of an easy-to-use portable electroencephalogram for long-term intermittent recording. Multiple studies have applied portable EEG solutions [50] to study usability, signal quality, performance, and electrode types, but there is no study providing information about the feasibility and acceptability of portable or wearable solutions during patients' independent long-term monitoring at home. EEG@HOME will provide for the first time a clear overview of participants' and developers' needs to enable "out-of-the-lab" EEG recordings using a portable solution with high compliance and high data quality.

Another key point of this procedure is the combination of multiple technologies to collect detailed data associated with seizure occurrence. Different studies have used self-reported information to study the association between factors such as sleep, mood or stress, and seizure occurrence. The influence of each of these varies between people and is not reliably predictive of seizure risk [51,52]. Other studies have used new wearable devices to collect physiological data associated with seizures. Despite this, a device capable of detecting multiple seizure types with acceptable sensitivity and specificity is currently not available, and the outcomes obtained by research studies are not generalizable to all people with epilepsy [53]. EEG@HOME will combine the use of all these solutions (wearable devices and smartphone app) in combination with continuous biosensor data and a self-reported diary to collect meaningful markers of seizure risk. It will provide a better understanding of the multifactorial nature of seizures, and the association between

these data could help in the identification of periods with a higher risk of seizure.

The identification of reliable information about seizure precipitants will also help people with epilepsy to avoid situations that could worsen seizures or cause seizure-related injuries. A continuous monitoring system that could detect seizures and trigger assistance might enhance safety for people with epilepsy [54]. It will increase the self-management and self-efficacy of people with epilepsy. It is well known that poor seizure control is associated with an increased incidence of depression and other mental health disorders [55] as well as an increase in family stress [56] and poor quality of life. It has also been shown that employment rates for people with epilepsy significantly improve to a level comparable to individuals who do not have epilepsy if they achieve good seizure control [57]. Placing people with epilepsy in a more active role in the monitoring and treatment of their condition may increase their quality of life and help them regain a sense of control despite the unpredictability of seizures [58].

EEG@HOME will provide a solution for health care providers and caregivers to easily monitor their patients' conditions and use the information acquired for better treatment decisions. In clinical practice, clinicians review seizure diaries and clinical history as a proxy for future seizure risk. Decisions about treatment are typically taken after a few months and multiple visits [59,60]. This approach is not the most efficient but is

unavoidable in the absence of a validated measure of future seizure risk.

The data set that will be created from the long-term monitoring during the EEG@HOME study will provide more information about the circadian and multiday patterns of seizure occurrence in epilepsy. Karoly and colleagues [5] found that 80% of people with epilepsy had significant and specific temporal cycles in their seizure activity. Most of the cycles were circadian (24 hours) and circaseptan (7 days), but some (approximately 20%) of the seizure cycles were longer than 3 weeks. Increasing the understanding of circadian and long-cycle factors may improve the sensitivity of future seizure prediction algorithms to inform more specific treatment schedules of traditional antiepileptic drugs for individual patients [3].

Finally, multiple factors related to the characteristics of people with epilepsy and device functionality that could affect the

experience of people with epilepsy during long-term monitoring will be assessed throughout the study. Having an overview of the main difficulties and critical factors will help in the design of future, larger, long-term studies.

Conclusion

For these reasons, EEG@HOME is an innovative and flexible procedure that will provide clear information for the design of future data acquisition trials for the at-home management of epilepsy and, potentially, other chronic neurological disorders. The continuous use of wearables and e-diaries will help people with epilepsy manage their condition and provide clinical professionals with reliable information to monitor and control their patients' therapy. This procedure will improve the interaction between people with epilepsy, caregivers, and health care providers. All the data collected will also allow the research team to have reliable information for the development of prediction algorithms and the design of future feasibility studies.

Acknowledgments

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Authors' Contributions

AB and MPR designed the study, coordinated its delivery, and wrote and amended the protocol for ethical approval and publication. EB, PFV, MS, and DKP contributed to reviewing the protocol for publication. PL developed an analytic method for handling the collected data. WH and EN contributed to the design and development of the Seer app for the collection of daily information. All authors have been involved in reviewing the manuscript and have given approval for it to be published.

Conflicts of Interest

EN and WH are employees of Seer Medical. MS is CEO of ANT Neuro GmbH and ANT Neuro UK Ltd. All other authors declare no conflicts of interest.

Multimedia Appendix 1

Peer Review Report.

[PDF File (Adobe PDF File), 372 KB - [resprot_v10i3e25309_app1.pdf](#)]

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Abbreviations

AUC: area under the receiver operating characteristic curve
BIPQ: Brief Illness Perception Questionnaire
BNI: brain network ictogenicity
EEG: electroencephalography
GCP: Good Clinical Practice
IED: interictal epileptiform discharges
NI: network ictogenicity
PSSUQ: Post-Study System Usability Questionnaire
SUS: System Usability Scale

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Protocol

A Smartphone App for Engaging Patients With Catheter-Associated Urinary Tract Infections: Protocol for an Interrupted Time-Series Analysis

Robbert Gerard Bentvelsen^{1,2}, MD; Karin Ellen Veldkamp¹, MD, PhD; Niels H Chavannes³, MD, PhD

¹Department of Medical Microbiology, Leiden University Medical Center, Leiden, Netherlands

²Microvida Laboratory for Medical Microbiology, Amphia Hospital, Breda, Netherlands

³Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, Netherlands

Corresponding Author:

Robbert Gerard Bentvelsen, MD

Department of Medical Microbiology

Leiden University Medical Center

Albinusdreef 2

Leiden, 2333 ZA

Netherlands

Phone: 31 7152 61652

Email: rbentvelsen@gmail.com

Abstract

Background: Catheter-associated urinary tract infections (CAUTIs) are the main cause of health care-associated infections, and they increase the disease burden, antibiotic usage, and hospital stay. Inappropriate placement and unnecessarily prolonged usage of a catheter lead to an elevated and preventable risk of infection. The smartphone app Participatient has been developed to involve hospitalized patients in communication and decision-making related to catheter use and to control unnecessary (long-term) catheter use to prevent CAUTIs. Sustained behavioral changes for infection prevention can be promoted by empowering patients through Participatient.

Objective: The primary aim of our multicenter prospective interrupted time-series analysis is to reduce inappropriate catheter usage by 15%. We will evaluate the efficacy of Participatient in this quality improvement study in clinical wards. Our secondary endpoints are to reduce CAUTIs and to increase patient satisfaction, involvement, and trust with health care services.

Methods: We will conduct a multicenter interrupted time-series analysis—a strong study design when randomization is not feasible—consisting of a pre- and postintervention point-prevalence survey distributed among participating wards to investigate the efficacy of Participatient in reducing the inappropriate usage of catheters. After customizing Participatient to the wards' requirements, it will be implemented with a catheter indication checklist among clinical wards in 4 large hospitals in the Netherlands. We will collect clinical data every 2 weeks for 6 months in the pre- and postintervention periods. Simultaneously, we will assess the impact of Participatient on patient satisfaction with health care services and providers and the patients' perceived involvement in health care through questionnaires, and the barriers and facilitators of eHealth implementation through interviews with health care workers.

Results: To reduce the inappropriate use of approximately 40% of catheters (currently in use) by 15%, we aim to collect 9-12 data points from 70-100 patients per survey date per hospital. Thereafter, we will conduct an interrupted time-series analysis and present the difference between the unadjusted and adjusted rate ratios with a corresponding 95% CI. Differences will be considered significant when $P < .05$.

Conclusions: Our protocol may help reduce the inappropriate use of catheters and subsequent CAUTIs. By sharing reliable information and daily checklists with hospitalized patients via an app, we aim to provide them a tool to be involved in health care-related decision-making and to increase the quality of care.

Trial Registration: Netherlands Trial Register NL7178; <https://www.trialregister.nl/trial/7178>

International Registered Report Identifier (IRRID): DERR1-10.2196/28314

(*JMIR Res Protoc* 2021;10(3):e28314) doi:[10.2196/28314](https://doi.org/10.2196/28314)

KEYWORDS

catheter-associated urinary tract infections; infection control; patient empowerment; urinary catheter; eHealth

Introduction

Background

Catheter-associated urinary tract infections (CAUTIs) are the main cause of health care-associated infections and lead to a higher disease burden, increased antibiotic usage, and prolonged hospital stay. Inappropriate placement and unnecessary prolongation of the use of a catheter lead to an elevated and preventable risk of infection.

The smartphone app Participatient has been developed to involve patients in communication and decision-making related to catheter use with the aim to overcome unnecessary (long-term) catheter use and prevent CAUTIs. Participatient can potentially empower patients to bring about sustained behavioral changes and prevent infections.

Previous Studies

Participatient was developed at Dutch Hacking Health Leiden 2016 as a prototype smartphone app to prevent CAUTIs by involving patients in health care-related decision-making. The jury awarded the Participatient development team with the first prize nationwide for developing a patient involvement interface with an innovative design for infection prevention.

Participatient engages patients by providing them with personalized information regarding the appropriateness of their catheter, along with other medical and admission-related information.

The prototype was further developed in collaboration with patients, hospital staff, social scientists, engineers, eHealth experts, infection control professionals, and clinical microbiologists. We invited patients and staff in clinical wards to express their needs and concerns and to test, rate, and provide feedback on the initial versions of Participatient and its content.

Through 3 rounds of improvements, based on 5-10 interviews with patients [1], and 2-4 nurses per round, we developed the final version of the app. The interviews were based on the technology acceptance model [2] based on the usefulness and the ease of use of the app and its features. Furthermore, we majorly focused on patients' skills in using technology and their eHealth literacy in order to increase the usability further [3,4]. The app was adjusted to the patients' requirements by including additional information, although this was optional so as to not cause inconvenience to those with eHealth experience.

This led us to (1) generate iconic graphics to clarify text, (2) use visual feedback intermezzos containing motivational text or an explanation of the results, (3) use plain language adjusted to the level of understanding of patients in general, (4) develop clickable and thus optional instructions in the questionnaire, and (5) disseminate practical information, which was most valued by patients in the hospital wards. The patient information leaflet was digitized in the app.

After the development phase, a proof-of-concept study was conducted at a clinical ward at Leiden University Medical Center (LUMC), in which the technical and interactive aspects of the app were tested. All patients admitted to this ward were invited to download the app for use during their hospital stay. The app was introduced to the patients by the nurse who managed patient admission. We actively supported app use and assessed and adjusted the app through feedback options and a questionnaire. Users expressed positive opinions about the app's purpose and design. We received some valuable feedback regarding the app's content, which was generated using the Catheter Check content module. Users scored the app with 5 out of 5 stars.

Participatient Content

During initial app use or "on-boarding," the patient is asked to provide information regarding their ward of admission, gender, age group, and previous internet or app usage. This information is used to provide directed information regarding their admission. The app can be downloaded from the Apple App store and Google Play store on a patient's smartphone or tablet device and comprises four content modules: Catheter Check, Admission Information, Pain Score, and Feedback. Finally, a Settings menu is included in the app (Figure 1).

Catheter Check is the catheter module, in which the appropriateness of catheter use is assessed by answering 8 questions. This yields a score in accordance with nationwide and worldwide criteria [5,6]. The result is displayed with personalized suggestions, promoting shared decision-making by motivating the patient to initiate dialogue with medical or nursing staff on the appropriateness of the presence of the catheter. Through daily reminders, patients are motivated to regularly check the indication of their catheter.

The Admission Information module comprises general medical information regarding infections, catheters, and the prevention of health care-associated infections for patients, but also practical information regarding the ward. From the patient feedback in the development phase, we learned that practical details including the visiting hours and telephone numbers of the ward were the most highly desired information. Participatient includes an information module with ward-specific information. In the proof-of-concept study, we used the patient information available in the ward's paper-based records and digitized it in the app to include images and links.

The Pain Score module yielded an adopted pain score that accounts for various factors including mobility, medication, and myths and facts on pain relief. This module motivated patients to ask for adequate pain medication and medication to combat side effects including nausea when needed. Pain score evaluation is not a part of this study proposal. Nonetheless, this module has been developed for better pain registration, advice and education on side effects, and motivation of patients to seek better pain management, leading to an enhanced health care experience. Through daily reminders, patients are motivated to regularly score their need for pain medication.

The Feedback module contains an 8-question survey on patient satisfaction with the app and a link for email communication with the researchers.

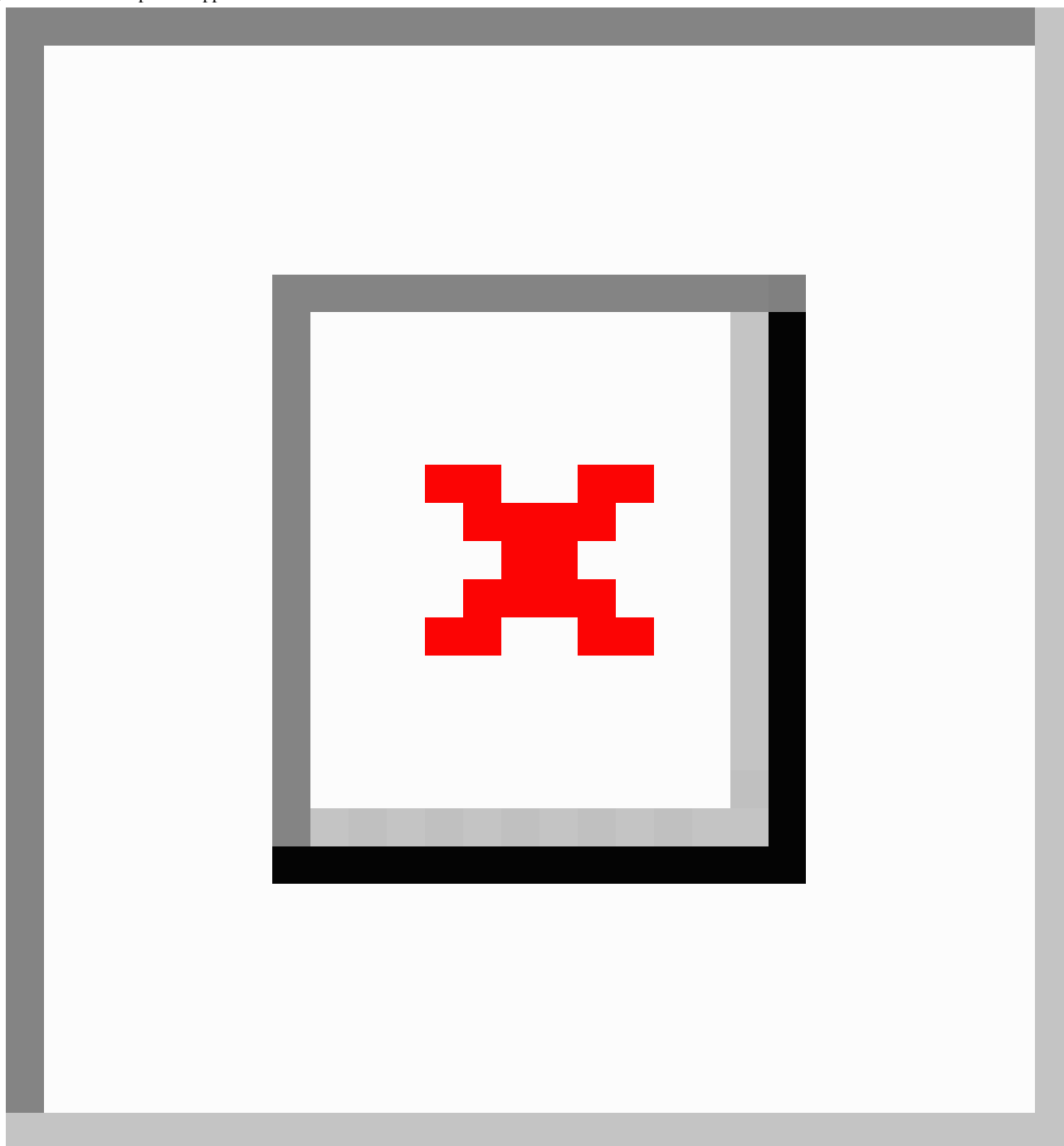
In the Settings module, the daily reminders can be adjusted or turned off, and basic demographic characteristics, including gender, age group, and specialty and ward of admission, can be visualized and modified.

Participatient is available free of cost to all patients in the participating hospitals. The costs of adjustment and deployment

are covered by the research team. App download and usage are limited by a code that is provided to the patients on admission.

Through the Admission Information and Pain Score modules in the app, users can avail of information and advice on other useful topics in addition to the catheter. In the development and proof-of-concept phases, users appreciated the additional functions of the app and indicated that this further motivated them to continue using the app throughout their hospital stay.

Figure 1. The Participatient app content.



Study Objective

During the implementation study, we aim to investigate whether the involvement of patients in infection prevention through an

eHealth tool is effective and sustainable. Our primary objective is to reduce catheters without an inappropriate indication in clinical wards by 15% by implementing Participatient.

Our secondary objectives are as follows: (1) to reduce CAUTIs; (2) to increase patient satisfaction with health care, their involvement in health care, and their trust in physicians; (3) to measure patient satisfaction with the usefulness and ease of use of Participatient and to optimize the app on the basis of these outcomes; and (4) to obtain analytical information regarding the use of various modules of the app and feedback from users for its further development and to make it available for extended use in preventing health care-associated infections or CAUTIs in primary and long-term care.

Methods

Overview

The app will be introduced in various clinical wards at 4 hospitals participating in the study. The app will be adjusted in accordance with the requirements of each medical center. Through a stepwise approach, we will launch the study at multiple locations.

The study will be implemented at clinical wards with a training session for the nurses in each ward, which will include a “kick-off” day that involves a demonstration of the app and an interactive session with the research team. We will provide information and instructions for downloading and installing the app on leaflets, which are normally provided to patients upon admission. Posters and flyers with infographics elucidating the risk of nosocomial infections and the study are provided to the participating clinical wards.

In each ward, we shall assess the willingness among and potential barriers to patients and health care workers. Before launching the app at each ward, it will be adjusted and extended to contain local information, protocols, and links to relevant websites of the 4 participating hospitals.

At each ward, an ambassador, with an affinity for the study, is recruited from among the nursing staff to provide peer support. This has been tested and found to be very useful in the proof-of-concept phase of this study. For active engagement of the ward staff, we included a regular support day in the ward for technical and medical troubleshooting during the implementation phase and the postintervention phase.

This is an interrupted time-series (ITS) analysis with the implementation phase between the pre- and postintervention survey. After the implementation phase, we will record feedback from the wards with regard to the prevalence and indication of catheters during the previous surveillance period. This “mirroring” technique is used in intervention studies and patient care to motivate subjects to facilitate further improvements. This would foster awareness and help reduce the use of catheters. Integration of an app in the health care routine is a complex intervention, with the implementation process itself also adding to the intervention. We will use the Trials of Intervention Principles Framework [7] to evaluate the overall effect of app implementation. During the postintervention

surveys, we will report data on app use per department. After the postintervention surveys, we will report the surveillance data per department and study site.

The Participatient website [8] contains general information regarding the study. For the implementation phase, the website will be revised and updated. After consulting patients and wards, we aim to provide relevant information from hospital admission to nosocomial infections. The relevant information provided in the app will be made available on the website.

Participating Hospitals

The following hospitals participated in this study: clinical wards of the LUMC (Leiden, the Netherlands), with the introduction of the app as main intervention; clinical wards of the Haaglanden Medical Center (The Hague, The Netherlands)—a regional general hospital—with the introduction of the app as the main intervention; clinical wards of the department of internal medicine and neighboring specialties of the Amsterdam University Medical Center (Amsterdam, The Netherlands) and the Spaarne Gasthuis (Haarlem, The Netherlands) as the second hospital from the Reduce the Inappropriate Use of Urinary and Intravenous Catheters study, with the app as an addition to the intervention bundle.

Patient Recruitment

All patients in the participating wards, aged ≥ 18 years, or their family members will be able to download the app from the Apple App store and Google Play store and use it on their personal smartphone or tablet device (Android, iPhone, or iPad devices). The patients and staff are included in each step of the process in accordance with the Patients Included charters on patient information resources.

Ethics Statement

All data are processed anonymously. The studies are and will be conducted in accordance with the tenets of the Declaration of Helsinki, and all procedures involving patients have been approved by the Medical Ethical and Institutional Review Board of the LUMC. Before conducting the interviews, distributing the questionnaires, or using the app, informed consent will be obtained, either in the verbal or written format in the case of interviews and paper-based questionnaires or in the digital format in the app before initial use, from all users to anonymize the data for analysis.

For clinical data on the improvement of care quality, consent will be obtained as described previously [6]. Patients are offered the option to opt out of the study at any time by being discharged by the treating physician, as stated in the hospital admission information [9].

Study Design

We will conduct a multicenter ITS consisting of a pre- and postintervention point-prevalence survey distributed among the participating wards to investigate the efficacy of the app in reducing the inappropriate use of catheters (Figure 2) [10].

Figure 2. Interrupted time-series analysis design with point-prevalence surveys (PPS).

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	
2018			Preparation				Pre-intervention 12x PPS						
2019	App	Postintervention 12x PPS						Analysis					



We will conduct the ITS as described previously [11]. Clinical data will be collected every 2 weeks for 6 months in the pre- and postintervention periods.

All admitted patients in the participating wards will be included in the point-prevalence survey regardless of app use, catheter presence, or urinary tract infection (UTI). A local study code will be generated for each patient for those with a catheter or a UTI. This code is a pseudonym to verify the collected data and rectify as required. This code will remain in the local hospital and only be used during the study.

During the point-prevalence surveys, the following data will be collected: demographic factors including gender, department and specialty of admission, age in decennia, and the date of admission; catheter use including the date of insertion of the catheter, indication of the catheter on insertion, and the indication of the catheter at the time of the survey; and UTI episodes occurring at the time of the survey and if a catheter was associated with them.

The presence and indications for catheter use will be extracted from the (electronic) medical records, nurses' lists, and observations of the admitted patients. On the day of measurement, the indication of the catheter and the necessary patient variables will be collected.

Measurement of Patient Satisfaction

To investigate the secondary outcomes, namely the impact of the app on patient satisfaction with health care services and providers and the patients' perceived involvement in health care, the following validated instruments will be included in the questionnaires. Paper-based questionnaires on satisfaction with care, trust in the physician, and communication will be distributed. These data will be collected along with additional data including gender, department and specialty, and age group. The questionnaire on patient satisfaction with the app will be administered through the app itself.

Satisfaction with care will be measured using the items of the Quality of Care Through the Patient's Eyes (QUOTE) questionnaire [12]. In total, 6 items will be used to measure patient satisfaction with the physician and nurse.

Trust in the physician will be measured using Trust in physicians_short form (TRIP_sf), which is based on the Cologne Patient Questionnaire scale to evaluate the patients' trust in physicians, which measures different aspects of trust during physician-patient interactions [13].

Self-efficacy during patient–health care provider communication will be measured with the 5-item version of the Perceived Efficacy in Patient-Physician Interactions (PEPPI-5) questionnaire, which assesses the subjective sense of patients' confidence when interacting with their physicians and patient involvement in health care [14,15].

To assess patient satisfaction with the app, a short 8-item evaluation questionnaire on the ease of use, time investment, usefulness, and perceived effect of the app will be used. Patient feedback will be requested through leaflets, and there will be a dedicated button on the home screen in the app.

Moreover, sociodemographic factors and general previous usage of eHealth or apps among patients will be measured [3,4] to determine the presence of patient features that predict the use and satisfaction with the app. To determine whether the app is fit for use by a wide range of users, user information will be requested upon on-boarding (initial use).

We will evaluate the health care workers' experience with the implementation of shared eHealth-related decision-making on the wards before and after comparison interviews to detect barriers and facilitators [16] in the wards at each center.

Analytical Data on App Use

Data on app usage and data obtained from the end users will be collected via the app and accompanying questionnaires. Usage data (analytics) on the number of downloads, the page views, and continued app usage will be collected. These data are traced to the users per ward, gender, internet or app experience, and age group, although they are not traceable to an individual level (privacy by design). User-provided data comprise the responses to the catheter check, pain score, and the use of the Admission Information module.

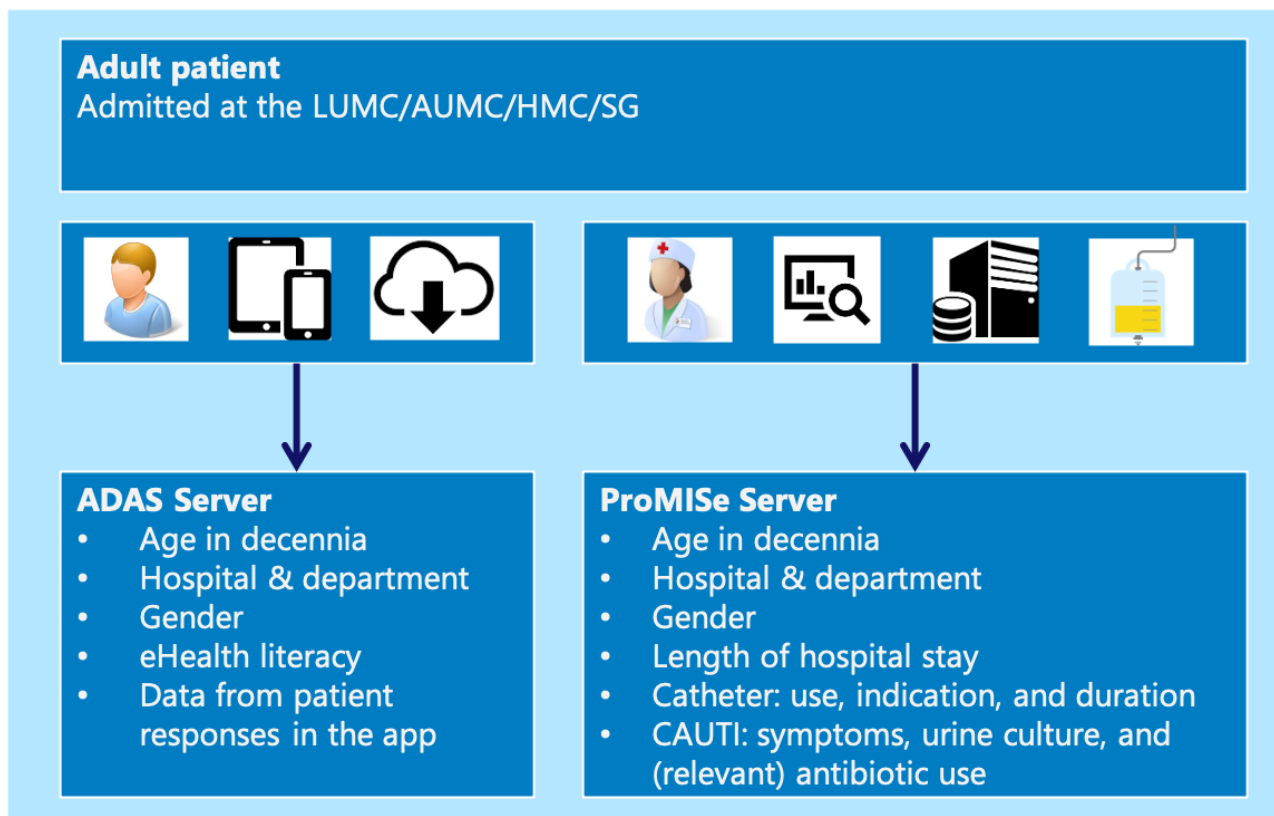
Data Management Plan

All data entered via the App will be stored with an anonymized ID in the app and on secure data management servers ADAS and ProMISe, which are located at the LUMC and managed by the Advanced Data Management section and are ISO 27001 certified. Data files used for analysis will be stored in the safe network storage facility DataSafe (Figure 3).

Data will be collected by the research physician (RB) at the LUMC. Participants will respond to the questionnaires. After

completion of a form, the app will contact the ADAS server of the LUMC and transmit the entered data, which is then stored as message files. These files are validated and transformed into requests for automatic data entry into the ProMISe server. The ProMISe server provides the functionality for data management, including data export to SPSS for statistical analysis, wherein an SPSS export will be performed, and these files will be stored in protected network storage (DataSafe) with access limited to the investigators.

Figure 3. Data collection and secure storage at the LUMC on ADAS and ProMISe servers. CAUTI: catheter-associated urinary tract infection, AUMC: Amsterdam University Medical Center; HMC: Haaglanden Medical Center; LUMC: Leiden University Medical Center; SG: Spaarne Gasthuis.



Analysis

Sample Size

The sample size is based on our objective of reducing inappropriate catheter use by 15%, with a power of 80% and a Cronbach α of .05. We extracted data on the incidence of inappropriate catheter use from previous studies in similar health care systems, which was approximately 40% for catheters [17,18]. We aim to collect 9-12 data points from among 100 patients per survey date per hospital [19,20]. On designating a particular day to obtain measurements every 14 days at each center, a 5-month period before and after the measurements is required. We intend to carry out surveys for 6 months and to collect 12 data points. At the LUMC, the prevalence of catheter use is approximately 30% among hospitalized patients, based on our pilot survey. Thus, 1200 patients are required per period, of whom catheters were used for 400 patients, and catheter usage being inappropriate among 160 patients. On correlating for 10%-15% of the missing data, the sample size is set to 1320-1380 patients in the pre- and postintervention groups. We

intend to include this number of patients at each hospital to analyze the effect of the interventions at each medical center.

Statistical Analysis

We will conduct an ITS analysis, similar to the one performed previously [21,22]. ITS is considered a strong study design when randomization is not possible and can thus be used to investigate causal effects with an observational “natural experiment” approach. The Cochrane collaboration guidelines for ITS analyses will be used with an autoregressive integrated moving average model [23]. Because such a model relies on linearity, we will assess the stationarity of the mean and variance with time through differencing [24,25]. The primary analysis involves a comparison of inappropriate catheter usage before and after Participant implementation. Because other changes in catheter usage could affect our outcomes over time, we will adjust the data for potential confounders, autocorrelation, and the underlying secular trend. Subgroup analyses will be performed on the basis of risk factors for catheters and UTIs, including the ward of admission, age group, internet or app use,

and gender. Analyses will be conducted using SPSS (version 24, IBM Corp).

We will use figures to visualize trends and the impact of the intervention. We will present the difference in unadjusted and adjusted rate ratios with a 95% CI. Differences will be considered significant when $P < .05$. All analyses, including subgroup analyses, will be predefined in an analysis plan before their performance.

For questionnaire assessment, we will use descriptive statistics and compare patient satisfaction with health care, their involvement in care, and their trust in physicians, before and after implementing the app. Data on patient satisfaction regarding the usefulness and ease of use of Participatient will be analyzed using descriptive statistics and will be used for subsequent rounds of app improvement after the study.

Results

Based on our objective of reducing the inappropriate use of approximately 40% of catheters by 15%, we aim to collect 9-12 data points from among 70-100 patients per survey date per hospital. We will conduct an ITS analysis, which is considered a strong study design when randomization is not feasible. We will present the difference in unadjusted and adjusted rate ratios with a 95% CI. Differences will be considered significant when $P < .05$.

Acknowledgments

We thank Dr TN Bonten (epidemiologist, LUMC) for assisting with the statistical design and Dr SE Geerlings (professor of internal medicine, Amsterdam University Medical Center) and Dr R van der Vaart (psychologist, Leiden University) for assisting in the study design. This study was funded by The Netherlands Organisation for Health Research and Development (522004007).

Conflicts of Interest

None declared.

Multimedia Appendix 1

Reviewer Comments B.2017.01BA0 from The Netherlands Organisation for Health Research and Development (ZonMw): project 522004007, dossier number 50-52200-98-559.

[[PDF File \(Adobe PDF File\), 65 KB - resprot_v10i3e28314_app1.pdf](#)]

Multimedia Appendix 2

Reviewer Comments B.2017.01BA1 from The Netherlands Organisation for Health Research and Development (ZonMw): project 522004007, dossier number 50-52200-98-559.

[[PDF File \(Adobe PDF File\), 64 KB - resprot_v10i3e28314_app2.pdf](#)]

Multimedia Appendix 3

Reviewer Comments B.2017.01BD2 from The Netherlands Organisation for Health Research and Development (ZonMw): project 522004007, dossier number 50-52200-98-559.

[[PDF File \(Adobe PDF File\), 59 KB - resprot_v10i3e28314_app3.pdf](#)]

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Discussion

This protocol describes the objectives, design, intervention, and survey methods for the “Patient Engagement Counter Catheter-associated urinary tract infections with an App” study and aims to prevent the inappropriate and prolonged use of catheters at acute care facilities.

A potential limitation of an ITS analysis is the lack of a control group. However, this quasi-experimental design is considered to be among the most effective and powerful designs when randomization is not feasible. Another limitation of this protocol is its inability to evaluate the impact of app use on an individual level. However, the intervention stimulates communication and creates awareness regarding the risks of inappropriate catheter use among all ward staff through patient engagement, thus benefiting all patients in the ward.

Thus far, patient involvement in infection prevention has been undervalued and unused as a means to improve the quality of care. By sharing reliable information and daily checklists to patients via an app, we can provide them a tool to involve them in the management of catheter use. Thus, inappropriate catheter use is expected to be better noticed and discouraged, and the risk of CAUTIs could be reduced.

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Abbreviations

CAUTI: catheter-associated urinary tract infection

ITS: interrupted time series

LUMC: Leiden University Medical Center

UTI: urinary tract infection

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Protocol

The Implementation Science for Genomic Health Translation (INSIGHT) Study in Epilepsy: Protocol for a Learning Health Care System

Elena Valeryevna Feofanova¹, MD, MSc, PhD; Guo-Qiang Zhang^{2,3,4}, MSc, PhD; Samden Lhatoo^{2,4}, MD, FRCP; Ginger A Metcalf⁵, BSc; Eric Boerwinkle^{1,5}, PhD; Eric Venner⁵, PhD

¹Human Genetics Center, Department of Epidemiology, Human Genetics and Environmental Sciences, School of Public Health, The University of Texas Health Science Center at Houston, Houston, TX, United States

²Department of Neurology, The University of Texas Health Science Center at Houston, Houston, TX, United States

³School of Biomedical Informatics, The University of Texas Health Science Center at Houston, Houston, TX, United States

⁴Texas Institute for Restorative Neurotechnologies, The University of Texas Health Science Center at Houston, Houston, TX, United States

⁵Human Genome Sequencing Center, Baylor College of Medicine, Houston, TX, United States

Corresponding Author:

Elena Valeryevna Feofanova, MD, MSc, PhD

Human Genetics Center

Department of Epidemiology, Human Genetics and Environmental Sciences, School of Public Health

The University of Texas Health Science Center at Houston

1200 Pressler St

RAS E-435

Houston, TX, 77030

United States

Phone: 1 713 500 982

Email: elena.v.feofanova@uth.tmc.edu

Abstract

Background: Genomic medicine is poised to improve care for common complex diseases such as epilepsy, but additional clinical informatics and implementation science research is needed for it to become a part of the standard of care. Epilepsy is an exemplary complex neurological disorder for which DNA diagnostics have shown to be advantageous for patient care.

Objective: We designed the Implementation Science for Genomic Health Translation (INSIGHT) study to leverage the fact that both the clinic and testing laboratory control the development and customization of their respective electronic health records and clinical reporting platforms. Through INSIGHT, we can rapidly prototype and benchmark novel approaches to incorporating clinical genomics into patient care. Of particular interest are clinical decision support tools that take advantage of domain knowledge from clinical genomics and can be rapidly adjusted based on feedback from clinicians.

Methods: Building on previously developed evidence and infrastructure components, our model includes the following: establishment of an intervention-ready genomic knowledge base for patient care, creation of a health informatics platform and linking it to a clinical genomics reporting system, and scaling and evaluation of INSIGHT following established implementation science principles.

Results: INSIGHT was approved by the Institutional Review Board at the University of Texas Health Science Center at Houston on May 15, 2020, and is designed as a 2-year proof-of-concept study beginning in December 2021. By design, 120 patients from the Texas Comprehensive Epilepsy Program are to be enrolled to test the INSIGHT workflow. Initial results are expected in the first half of 2023.

Conclusions: INSIGHT's domain-specific, practical but generalizable approach may help catalyze a pathway to accelerate translation of genomic knowledge into impactful interventions in patient care.

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KEYWORDS

genomic medicine; electronic health record; implementation; genetics; prototype; decision support

Introduction

Despite enormous progress in gene discovery and the prioritization of research objectives related to precision medicine, translation of this rich body of scientific knowledge into standard patient care has been slow. Clinical genomics is emerging as a standard of care, with more than 60% of US private payers covering multigene testing in cancer [1] and in congenital anomalies and neurodevelopmental disorders in children [2]. Whole exome sequencing (WES) produces a considerable diagnostic yield (DY) and results in meaningful clinical management changes in a number of heritable diseases, including cardiomyopathies (DY=12%-50%) [3-5], chronic kidney disease (DY=10%-24%) [6-8], neuromuscular diseases (DY=39%) [9], hearing impairment (DY=33.5%) [10], primary immunodeficiency (DY=56%) [11], hematological disorders (DY=17%-23% for bleeding diathesis and pediatric platelet disorders) [12,13], monogenic conditions (DY=25%-58%) [14], and lung and colorectal adenocarcinomas (DY for the germ-line mutations ~5%; DY for somatic mutations ~30%) [15]. In epilepsy, WES provides a DY of approximately 45% [16-18], with approximately 40% of these having potential treatment implications [19,20].

Overall, the number of genetic studies, with ever-increasing sample sizes and discovery rates, have been growing [21]. At the same time, it has been estimated that 3% or less of the published research is focused on development and integration of evidence-based guidelines into clinical practice [22], with an average of 17 years passing between obtaining scientific evidence and its integration into clinical care [23]. Further, broad implementation of genomics information into standard clinical practice faces a significant gap in management velocity, defined as the time taken for new information to initiate change or to advance diagnosis and/or treatment.

In the area of genomic medicine, we are addressing the management velocity gap by building software and workflows between point of clinical care, the sequencing laboratory, variant interpretation, electronic health records (EHRs), and clinical decision support, thus streamlining the process of ordering, sample collection, sequencing, interpretation, and return of results. The benefit is identification of clear care pathways for placing testing into routine health care, with implications generalizable to other complex diseases. We designed the communication pathways to ensure that clinicians have access to interpreted genetic data and that rich phenotyping is available for researchers to mine for new diagnostic and prognostic discoveries. In particular, mining phenotype data from EHRs has been shown to be especially useful [24].

Several features of epilepsy set epilepsy care apart from many other conditions, making it an ideal setting in which to develop novel user-oriented EHR systems. This complex chronic neurological disease affects 50 to 60 million people worldwide and 3 million lives in the United States [25,26]. The high prevalence of epilepsy is in contrast to lower prevalences of

neuromuscular diseases (1 to 10 per 100,000 people) [27], hypertrophic (estimated 98,958 cases in the United States) and dilated (1 in 250 to 1 in 500 adults) cardiomyopathies [28,29], all lung cancer cases (n=571,340), and all colon and rectum cancer cases (n=1,544,570) [30]. Only hearing loss has a higher prevalence of approximately 60.7 million people in the United States [31], but cannot compare in the severity of the loss of quality of life. Epilepsy affects people of all ages, with bimodal age incidence peaks in early life and in the elderly and the greatest prevalence in adult and young adult populations [25,32]. Thus, it is an excellent model for clinical genomics knowledge integration spanning pediatric, adult, and geriatric clinical care settings. In contrast, colon and lung cancer, chronic kidney diseases, and cardiomyopathies are predominantly seen in older adults [29,30]. Half of all patients with epilepsy have medical, psychiatric, and/or cognitive comorbidities [33,34], requiring evidence-based management interactions as genomic knowledge accrues. Multiple treatment approaches are available for epilepsy management, ranging from ketogenic diets to surgery, in contrast to neuromuscular diseases, which are predominantly managed by immunotherapy [35], and cancer, which usually requires a surgical intervention [36].

Around one-third of epilepsy patients are unresponsive to antiepileptic drugs (AEDs) [37], similar to other heritable drug-resistant conditions (eg, early-onset inflammatory bowel diseases) [38,39]. Adverse drug reactions (ADRs) are seen in 6% to 7% of all hospital admissions, include life-threatening reactions, and remain a vexing issue in epilepsy management [40]. One-third of all AEDs have known pharmacogenomics (PGx) loci [41,42]. Information on a patient's genetic status for these loci can predict occurrence of ADRs and affect a clinician's management strategy [41,42]. Epilepsy can model the adaptation of actionable PGx into clinical settings for other diseases, with lessons learned impacting the data presentation, decision support, and reanalysis as guidelines are updated. Moreover, there are many heterogeneous subtypes of epilepsy that are difficult or impossible to distinguish without molecular data. Genomic data can aid in diagnosis, but are also prone to discovery of variants of unknown significance (VUS) [43]. In turn, EHR data contain a rich phenotype allowing for improved variant interpretation [44], which can help reduce VUS.

However, traditional EHR systems, such as Epic and Cerner, do not allow for genomic information to be entered in a structured, action-ready format [45]; such integration involves expensive customization and workflow reconfiguration efforts and costs, representing fundamental barriers [45]. As such, systems were not designed to take advantage of the latest genomic medicine advances, nor are they amenable to prototyping multiple approaches to optimize the presentation and collection of data. Hence, there is a need for exemplary user-oriented systems built to prototype and evaluate EHR functionality. In this project, we seize the unique opportunity presented by our control over the development of EHR and clinical reporting environments to integrate genomic knowledge

with phenotypic information and evaluate its clinical utility, and propose an adaptable clinical genomics workflow design.

Methods

Development of Health Data Management Platforms

To bring together the epilepsy clinic and clinical genomics information, a connection needs to be established between respective health data management platforms. Previously, we developed the Epilepsy Tracking and optimized Management engine (EpiToMe), an EHR system customized for epilepsy care, to address common EHR challenges, such as inability to handle specialty-specific documentation requirements [46]. EpiToMe uses agile, physician-centered development to optimize clinical workflow and ease patient care documentation and billing [46]. EpiToMe captures data in clinical research-ready form and links it with hospital EHR systems, while providing integrated interfaces for patient tracking, report generation, structured data capture for electroencephalogram (EEG) reporting, daily video-EEG reporting, and comprehensive presurgical phase reporting for Epilepsy Monitoring Units (EMUs). This is achieved using a metadata-anchored approach: we used the Epilepsy and Seizure Ontology as the semantic anchor for implementing all front-end and back-end capabilities of EpiToMe. Operationalization of EpiToMe at the University of Texas Health Science Center at Houston (UTHealth) (an Epic site) and Memorial Hermann Health System (a Cerner site) since February 2019 has demonstrated its effectiveness to support clinical workflows, with 21,456 EEG reports, 4534 EMU daily reports, and 2635 EMU phase reports completed.

The Human Genome Sequencing Center's (HGSC) clinical reporting platform, Neptune, enables identification and reporting of known disease-causing variants in gene sets of interest, the curation of potential novel pathogenic variants, and sharing of important—or VIP—variants with clinical partners. Neptune searches for each sample's genomic variants in a curated database, currently containing 381,564 variants annotated with a wide array of information drawn from public resources (ie, ClinVar, Online Mendelian Inheritance in Man [OMIM], and literature review) and internal curation data sets. If all variants are properly curated, Neptune allows for automated reporting and produces a clinical report containing pathogenic single-nucleotide variants and copy number variants, other project-specific report elements (eg, PGx output and polygenic risk scores), descriptive text, coverage statistics produced by the HGSC's Exome Coverage and Identification Report software, and other required reporting elements (eg, sample metadata and methodology) for review and approval by a laboratory director. Neptune has been applied to Electronic Medical Records and Genomics (eMERGE) III and HeartCare samples, with more than 15,000 clinical reports generated to date [47,48]. Neptune supports a variety of output formats, including human-readable HTML and PDF as well as structured JavaScript Object Notation (JSON), XML, and Fast Healthcare Interoperability Resources (FHIR) formats. The eMERGE III project addressed a similar challenge: to create a functioning network of existing clinical laboratory reporting systems and clinical site EHRs [48]. Key lessons from this project were the

importance of using open interoperability standards, of designing around regular updates to genomic data, and of structured genomic data for clinical decision support.

Last, the importance of genetic information in routine cardiovascular health management has been demonstrated through our earlier HeartCare gene panel. Pilot-testing in 700 participants resulted in identification of pathogenic and likely pathogenic variants (8%), identification of PGx loci (51%) [47], and prompting clinical management changes, including medication and imaging (6%), referral (15%), and additional laboratory testing (79%).

Integrated Clinical Genomics Platform

An adaptable clinical genomics workflow requires formation of an integrated clinical genomics platform, which consists of two stages, as described below.

Intervention-Ready Genomic Knowledgebase

Epilepsy patients are routinely assessed with magnetic resonance imaging, blood tests, EEG, and, occasionally, urine tests and skin biopsies. Additionally, AED prescriptions entail monitoring of AED and sodium levels, blood counts, and liver and bone function [49-52]. These tests provide data essential for an initial diagnosis and reside in the EHR. EpiToMe schema can be extended to store existing phenotype data alongside genomic information, thus linking patient records with gene and variant-level annotations (eg, inheritance pattern, gene-disease association, drug-gene PGx pairs, mutational effect, variant interpretation, associated evidence codes, and literature; see [Multimedia Appendices 1 and 2](#)). Since genomic annotations change often, our model includes keeping annotations up to date and providing reports and alerts of important changes. This involves identification and creation of mappings for test results to Human Phenotype Ontology (HPO) terms [53,54], with automatic transfer to Neptune. Existing HPO-gene mappings can be employed for genes prioritization [55]. Subsequently, this resource can be used to develop electronic phenotyping to detect patients who are likely to benefit most from genetic analysis.

Health Informatics Platform and Systems Coupling

We designed a health informatics platform called EpiToMe+ that brings the Intervention-Ready Genomic Knowledgebase (iRGK) to bear with clinical decision support and patient care. To achieve a genomics-integrated epilepsy care system, EpiToMe+ is designed to extend capabilities as follows:

1. Expand clinical report interfaces with a genomic variants report [46], which is designed to reflect the status and contents of biospecimen obtainment and genetic report steps of the clinical genomics workflow.
2. Add a genetic testing step to the tracker—an interactive, real-time interface—displaying patient status in the epilepsy care workflow [46].
3. Integrate iRGK for actionable PGx loci into EpiToMe's clinical report [46], with built-in notification when an AED with a known actionable PGx locus present in the patient is prescribed, to help improve patient management.

- Clinical laboratory information, prescribed medications, exam data, patient history, and genetic information are then transmitted from Cerner and Epic systems, using Health Level Seven International (HL7) messaging, and are used for ADR prediction and identification [56,57].
- Trained statistical models for ADR prediction on available EpiToMe data can then be incorporated to produce a

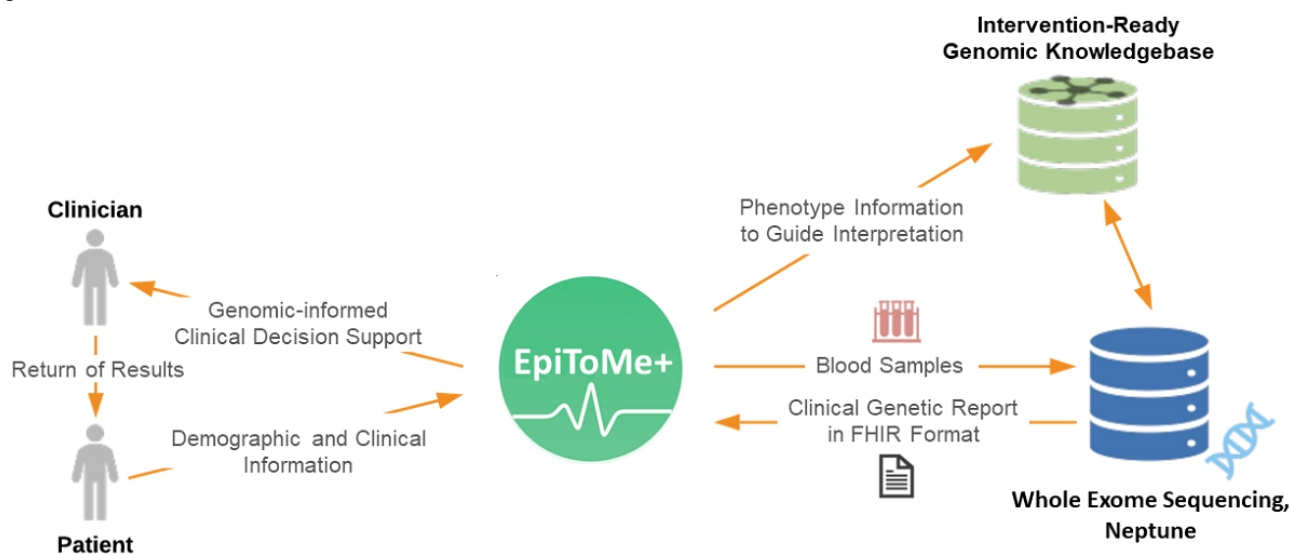
summary of the estimated risks of ADRs, as well as existing risk factors, to support clinical decision making [58,59].

Integration between Neptune and EpiToMe+ enables genomic data to be acted upon at the point of care.

Clinical Genomics Workflow

Our overall clinical workflow consists of five steps (see Figure 1).

Figure 1. Clinical genomics workflow. The Implementation Science for Genomic Health Translation (INSIGHT) project has been designed to connect two existing clinical informatics systems: Epilepsy Tracking and optimized Management engine (EpiToMe), a bespoke epilepsy-specific electronic health record system, and Neptune, a clinical genomics reporting pipeline. To pilot this system, 120 patients from the Texas Comprehensive Epilepsy Program for whole exome sequencing are to be recruited. Their genetic data are designed to be generated and analyzed at the Human Genome Sequencing Center and returned via Fast Healthcare Interoperability Resources (FHIR) messages to EpiToMe+, where it can be presented at the point of care, with clinical decision support. A new knowledge base, Intervention-Ready Genomic Knowledgebase, is designed to form the back end, enabling this integration.



Demographic and Clinical Information

During a patient visit, demographic and clinical information is created and updated through EpiToMe's existing HL7 messaging with a parent EHR. Clinical reports interface into EpiToMe, capturing patient information, including EEG reporting, phase reporting, daily care reporting, and evoked potentials [46]. HL7 is a widely used framework and interoperability standard for clinical and administrative data transmission between EHR systems [60]. HL7 engine design ensures seamless transfer of obtained data between EpiToMe and the parent EHR [46].

Blood Samples

Blood is drawn following consent and sent to the HGSC Clinical Laboratory. DNA extraction and biobanking is performed during this step.

Sequencing, Genomic Analyses, and Interpretation

Sequencing, genomic analyses, and interpretation are performed at the HGSC with results stored in Neptune. Sample preparation and sequencing are followed by mapping, alignment, and variant calling using standard clinical pipelines. Neptune selects novel variants according to reporting requirements for review according to American College of Medical Genetics (ACMG) guidelines [61]. For each sample, a deidentified clinical report is developed to contain clinically relevant variants and PGx loci

for AEDs to help improve patient management. Pharmacogenomic alleles are detected by force-calling genotypes according to their definitions in the Clinical Genetics Implementation Consortium (CPIC) and/or the Pharmacogenomics Knowledge Base (PharmGKB). For the challenging cytochrome P450 2D6 (Cyp2D6) region, we anticipate validating the DRAGEN Cyp2D6 caller [62]. Our reports are designed to focus on gene-drug pairs with CPIC evidence levels A and B and/or PharmGKB levels 1A to 2B, especially those with existing therapeutic management recommendations according to the US Food and Drug Administration (see Multimedia Appendix 2) [41,42,63]. After review and approval by an ACMG-boarded lab director, the report is then transferred in a structured format to UTHealth for final report rendering and storage in the iRGK. Last, a local disease-specific reference library is designed to reflect current knowledge in the field to inform genetic analyses and clinical decision support.

Clinical Genetic Report

Reports of relevant genomic variants are sent from Neptune to EpiToMe+ using the HL7 FHIR genomic format. The previously developed HL7 FHIR is a rising standard for clinical genomics reporting [45,60,64], which can be adopted for structuring the required genomic data (ie, single-nucleotide variants, indels, copy number variants, and PGx), with revisions to the HL7

Clinical Genomics Work Group to be recommended as necessary. An FHIR-based interface enables reports of genomic variants transmitted to EpiToMe+ for automatic storage and reflection in genomic reports for individual patients. We designed system-to-system coupling to connect genomic reports with other clinical information so that the patient's clinical information can be used to inform the interpretation of genetic results and to capture phenome-genome interactions within the EHR data. For example, the use of existing biochemical data can lead the reviewer to specific gene pathways, which, in turn, may help with disease stratification. This step also addresses the genetic information storage issue, since traditional EHR systems are not prepared to accommodate the complete genetic results, which tend to be bulky [45]. The EpiToMe architecture ensures effective and secure storage of patients' data.

Clinical Decisions and Return of Results

The resulting clinical decisions and care are provided by epilepsy physicians trained to effectuate available clinical genomic knowledge. Return of clinical genomics results (ie, return of results [RoR]) for common chronic diseases is challenging. We found previously that for positive findings, clinicians prefer to perform RoR personally, due to their close relationships with the patient (manuscript in preparation). Further, 40% of epilepsy patients have psychiatric comorbidities [65], and clinicians are trained to handle complex clinical care scenarios. In addition, physicians are generally not sufficiently prepared to integrate genetic test results into clinical care, with continuing professional development being particularly important [66]. Genetic counselors, although extensively trained for Mendelian disorders, birth defects, inherited cancer, and inborn errors of metabolism, may lag behind the expanding knowledge in other areas, and collaborations between genetic

counselors and clinicians can ensure adequate interpretation of genetic information [67].

In our model, negative findings are returned in a form letter, positive findings are returned by the patient's clinician, and in cases of complex genetic disease or high heritable risk, patients are referred for genetic counseling. Our model also includes "scripts" that guide clinicians through common findings. For instance, for carriers of the G allele of rs121964976 (*GLDC*, ClinVar No. VCV000011985), recommendations can include a ketogenic diet, protein restriction, or sodium benzoate [68,69], while patients carrying rare pathogenic *POLG* alleles, such as rs113994098 (ClinVar No. VCV000013502.10), should not be prescribed valproate for seizure control (see [Multimedia Appendices 1 and 2](#)) [63,70]. Further, the effectiveness with which clinicians return genetics test results can be measured by assessing, for example, the level of comprehension following RoR.

Compared to other existing clinical genetics workflows, such as those developed for HeartCare, All of Us, eMERGE, and rapid newborn intensive care unit projects, Implementation Science for Genomic Health Translation (INSIGHT) stands out due to the high positive rate in epilepsy and availability of detailed EHR phenotyping (see [Table 1](#)). It follows the best practices for the RoR and report contents. The usage of WES in INSIGHT is designed to allow for genetic data reanalysis for epilepsy, as well as for other diseases, and harbors a possibility for future research, extending beyond the preselected genetic loci in panel-based projects. The challenges, including phenotype collection and RoR approach, are shared across disease areas and projects. The multimodality aspect of epilepsy makes INSIGHT generalizable to other disease areas, further strengthening the case for INSIGHT as an exemplary clinical genetics workflow.

Table 1. Comparison of the main characteristics of selected clinical genetics workflows.

Workflow characteristic	HeartCare	All of Us	eMERGE ^a	INSIGHT ^b	Rapid NICU ^c
Genetic test type	Panel	Panel	Panel	WES ^d	WGS ^e
Approximate positive rate, %	8	~2-3	3	>40	>30
Up-front phenotype term collection	Main disease areas	None	Main disease areas	Detailed	— ^f
Return of results					
Return of results by clinician	Yes	No	No	Yes	Yes
Return of results by genetic counselor	Partial	Yes	Yes	Partial	Yes
Report characteristics					
Form of report is easily EHR ^g -integratable	Yes	Somewhat	Yes	Yes	Yes
Report is focused on one disease area	Yes	No	No	Yes	No
Report contains pharmacogenomics	Yes	Yes	Yes	Yes	Yes
Report contains polygenic risk score	Yes	No	No	No	No
Usage of genetic information					
Reanalysis of genetic information desired	Yes	Yes	Yes	Yes	Sometimes
Reanalysis enables future diagnosis on other diseases	No	Yes	Yes	Yes	Yes
Supports genotype-phenotype analysis	Yes	Yes	Yes	Yes	Yes
Generalizability					
Overall reporting framework generalizable to other diseases	Yes	Yes	Yes	Yes	Yes
Generalization <i>requires</i> development of specialty-specific systems	No	No	No	No	No

^aeMERGE: Electronic Medical Records and Genomics.

^bINSIGHT: Implementation Science for Genomic Health Translation.

^cNICU: neonatal intensive care unit.

^dWES: whole exome sequencing.

^eWGS: whole genome sequencing.

^fProject is in development and data are not available.

^gEHR: electronic health record.

Results

INSIGHT was approved by the Institutional Review Board of UTHealth on May 15, 2020. It is designed as a 2-year study, set to start in December 2021. Activities of the first year consist of system testing, integration, and iRGK development. Activities of the second year include enrollment of 120 patients from the Texas Comprehensive Epilepsy Program to pilot-test the INSIGHT clinical genomics workflow, exercise communication between Neptune and EpiToMe+, identify integration bottlenecks, and validate the EpiToMe+ genomic reporting and clinical decision support interfaces. Following the principles of implementation science, this pilot is designed to undergo an evaluation and modification period prior to further scaling of the INSIGHT program. EpiToMe+ is designed to continually trace patient-level outcomes (seizure control, adverse event incidence, etc), to measure value of implementation (eg, genetic results turnaround time, clinician interactions with decision support tools, and response to PGx prescription notifications), and to guide improvement in quality and effectiveness of use

of clinical genetics health services. The results of the study are expected in the first half of 2023.

Discussion

We present a workflow and software, named INSIGHT, for integrating genomics into routine clinical care. INSIGHT is designed to allow evaluation of model data structures and infrastructure frameworks for an integrated clinical genomics platform, allowing for genetic testing, data incorporation, results interpretation, and clinical decision support, which can be universally applied. Epilepsy exemplifies various modalities of care and is a suitable exemplar to demonstrate innovation, feasibility, and potential clinical impact for patient care. Therefore, lessons learned will be applicable to a number of conditions in which clinical genomics already show promise (eg, cardiomyopathies, certain kidney and digestive disorders, and a list of familial or early-onset cancers). Additionally, our design includes assessment of the feasibility of adopting and extending existing data standards to integrate disparate data types into a single knowledge base. INSIGHT is designed to

help catalyze a pathway to accelerate translation of genomic knowledge into impactful clinical intervention and patient care practice and to promote discovery.

It is, nonetheless, important to consider limitations of INSIGHT. First, some of its aspects are specific to epilepsy, which might raise questions about the generalizability of the tools. It is important to note that INSIGHT is generalizable and adaptable to other disease specialties in the following key aspects:

1. The conceptual architecture identifies and connects previously independent system components in disparate domains through a synergistic flow of data and information that can help drive the velocity of management.
2. The system interconnect leverages standard messaging formats, such as FHIR and HL7.
3. EpiToMe+ contains generalizable and reusable software components and interface innovations.
4. Neptune is an open source software [71] and has been applied to clinical reporting for a wide variety of disease contexts, including cardiac disease (ie, dyslipidemias, arrhythmias, and cardiomyopathies), breast and colon cancers, as well as samples with no indication for testing.

Second, creation of a VIP database for any disease area from the ground up requires a significant investment of time and resources. For the epilepsy-related genes, our primary focus will be on the potentially actionable genes, especially those having been reviewed by the ClinGen Epilepsy Gene Curation Expert Panel. By design, we will take into consideration the ACMG pathogenic and likely pathogenic variants reported to ClinVar. Hence, the VIP database for epilepsy is designed to be built on the available evidence and previous work and will be evolving over time.

The timeline for recruitment, data collection, sequencing, and RoR for 120 patients is designed to be relatively short. Fortunately, the epilepsy clinic of the Texas Comprehensive Epilepsy Program sees more than 600 new patients per year referred from the Greater Houston Metropolitan Area and elsewhere. Currently, less than 10% of patients undergo genetic testing. It is the goal of INSIGHT to follow an implementation science framework to scale genetic testing to be part of routine care. INSIGHT is designed to focus on intractability and focal or generalized epilepsy severity, defined by the presence of convulsive seizures at least once a month, since it is this group that is likely to benefit the most from genetic analysis and targeted treatments that promise greater efficacy as well as obviate ADRs. Besides, sequencing coverage is always a concern for tests based on next-generation sequencing. We have identified 1909 genes related to epilepsy and assessed their coverage in our Clinical Laboratory Improvement Amendments–validated exome assay. A total of 96% of coding regions defined by these genes have at least 20 times coverage, and 98.5% receive at least 10 times coverage.

In conclusion, there is a need for exemplary user-oriented systems built to prototype and evaluate EHR functionality in the genomics context. The development cycles for EHR systems are long, so prototyping new feature sets and evaluating them in a clinical context is an important avenue for speeding up the deployment of genomic medicine. The resource described here, embedded with the adaptable clinical workflow design, is designed to place a body of translational knowledge in the context of precision intervention in patient care, allowing us to benchmark and optimize its delivery.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Genes known to cause epilepsy and the corresponding existing and emerging therapeutic approaches.

[PDF File (Adobe PDF File), 681 KB - [resprot_v10i3e25576_app1.pdf](#)]

Multimedia Appendix 2

Known pharmacogenomics loci in epilepsy.

[PDF File (Adobe PDF File), 486 KB - [resprot_v10i3e25576_app2.pdf](#)]

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Abbreviations

ACMG: American College of Medical Genetics
ADR: adverse drug reaction
AED: antiepileptic drug
CPIC: Clinical Genetics Implementation Consortium
Cyp2D6: cytochrome P450 2D6
DY: diagnostic yield
EEG: electroencephalogram
EHR: electronic health record
eMERGE: Electronic Medical Records and Genomics
EMU: Epilepsy Monitoring Unit
EpiToMe: Epilepsy Tracking and optimized Management engine
FHIR: Fast Healthcare Interoperability Resources
HGSC: Human Genome Sequencing Center
HL7: Health Level Seven International
HPO: Human Phenotype Ontology
INSIGHT: Implementation Science for Genomic Health Translation
iRGK: Intervention-Ready Genomic Knowledgebase
JSON: JavaScript Object Notation
OMIM: Online Mendelian Inheritance in Man
PGx: pharmacogenomics
PharmGKB: Pharmacogenomics Knowledge Base
RoR: return of results
UTHealth: the University of Texas Health Science Center at Houston
VUS: variants of unknown significance
WES: whole exome sequencing

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Protocol

Longitudinal Cohort Study of Gender Affirmation and HIV-Related Health in Transgender and Gender Diverse Adults: The LEGACY Project Protocol

Sari L Reisner^{1,2}, ScD; Madeline B Deutsch³, MD, MPH; Kenneth H Mayer^{2,4,5,6}, MD; Jennifer Potter^{2,5,6}, MD; Alex Gonzalez^{2,5,6}, MD; Alex S Keuroghlian^{2,5,7}, MD, MPH; Jaclyn MW Hughto^{8,9}, MPH, PhD; Juwan Campbell⁵, MA; Andrew Asquith⁵, BA; Dana J Pardee⁵, BS; David R Pletta⁵, MPH; Asa Radix¹⁰, PhD, MD

¹Division of Endocrinology, Diabetes and Hypertension, Brigham and Women's Hospital, Boston, MA, United States

²Harvard Medical School, Boston, MA, United States

³University of California San Francisco, San Francisco, CA, United States

⁴Harvard TH Chan School of Public Health, Boston, MA, United States

⁵The Fenway Institute, Boston, MA, United States

⁶Beth Israel Deaconess Medical Center, Boston, MA, United States

⁷Massachusetts General Hospital, Boston, MA, United States

⁸Brown University School of Public Health, Providence, RI, United States

⁹Center for Health Promotion and Health Equity, Brown University, Providence, RI, United States

¹⁰Callen-Lorde Community Health Center, New York, NY, United States

Corresponding Author:

Sari L Reisner, ScD

Division of Endocrinology, Diabetes and Hypertension

Brigham and Women's Hospital

221 Longwood Ave

Boston, MA, 02115

United States

Phone: 1 (617) 732 5666

Email: sreisner@bwh.harvard.edu

Abstract

Background: Transgender and gender diverse (TGD) adults in the United States experience health disparities, especially in HIV infection. Medical gender affirmation (eg, hormone therapy and gender-affirming surgeries) is known to be medically necessary and to improve some health conditions. To our knowledge, however, no studies have assessed the effects of gender-affirming medical care on HIV-related outcomes.

Objective: This study aims to evaluate the effects of medical gender affirmation on HIV-related outcomes among TGD primary care patients. Secondary objectives include characterizing mental health, quality of life, and unmet medical gender affirmation needs.

Methods: LEGACY is a longitudinal, multisite, clinic-based cohort of adult TGD primary care patients from two federally qualified community health centers in the United States: Fenway Health in Boston, and Callen-Lorde Community Health Center in New York. Eligible adult TGD patients contribute electronic health record data to the LEGACY research data warehouse (RDW). Patients are also offered the option to participate in patient-reported surveys for 1 year of follow-up (baseline, 6-month, and 12-month assessments) with optional HIV and sexually transmitted infection (STI) testing. Biobehavioral data from the RDW, surveys, and biospecimen collection are linked. HIV-related clinical outcomes include pre-exposure prophylaxis uptake (patients without HIV), viral suppression (patients with HIV), and anogenital STI diagnoses (all patients). Medical gender affirmation includes hormones, surgeries, and nonhormonal and nonsurgical interventions (eg, voice therapy).

Results: The contract began in April 2018. The cohort design was informed by focus groups with TGD patients (n=28) conducted between August-October 2018 and in collaboration with a community advisory board, scientific advisory board, and site-specific research support coalitions. Prospective cohort enrollment began in February 2019, with enrollment expected to continue through August 2020. As of April 2020, 7821 patients are enrolled in the LEGACY RDW and 1756 have completed a baseline survey.

Participants have a median age of 29 years (IQR 11; range 18-82). More than one-third (39.7%) are racial or ethnic minorities (1070/7821, 13.68% Black; 475/7821, 6.07% multiracial; 439/7821, 5.61% Asian or Pacific Islander; 1120/7821, 14.32% other or missing) and 14.73% (1152/7821) are Hispanic or Latinx. By gender identity, participants identify as 33.79% (2643/7821) male, 37.07% (2900/7821) female, 21.74% (1700/7821) nonbinary, and 7.39% (578/7821) are unsure or have missing data. Approximately half (52.0%) of the cohort was assigned female sex at birth, and 5.4% (421/7821) are living with HIV infection.

Conclusions: LEGACY is an unprecedented opportunity to evaluate the impact of medical gender affirmation on HIV-related health. The study uses a comprehensive research methodology linking TGD patient biobehavioral longitudinal data from multiple sources. Patient-centeredness and scientific rigor are assured through the ongoing engagement of TGD communities, clinicians, scientists, and site clinical staff undergirded by epidemiological methodology. Findings will inform evidence-based clinical care for TGD patients, including optimal interventions to improve HIV-related outcomes.

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KEYWORDS

cohort studies; transgender persons

Introduction

Background

In the United States, transgender and gender diverse (TGD) adults experience disparities in HIV-related outcomes, particularly TGD women who have an estimated 21.7% laboratory-confirmed HIV prevalence (meta-analysis), a 34.2-fold increased odds relative to the US general population [1]. Black and Latinx TGD people are particularly hard-hit by the HIV epidemic [2,3]. TGD men are also at risk for HIV acquisition and transmission, particularly TGD men who are gay, bisexual, or have sex with other men [2,4-7]. Data are lacking about the HIV epidemic in nonbinary TGD people [3,4]. TGD people are a priority population for HIV biobehavioral prevention and care efforts [8]. HIV testing is vital in identifying new HIV infections and linking TGD individuals to antiretroviral treatment [8]. Pre-exposure prophylaxis (PrEP) has shown efficacy in reducing HIV incidence in TGD people without HIV, offering options for clinically delivered prevention interventions [9]. There is substantial variability in viral suppression rates among TGD people with HIV (eg, 50%-81%) [10-12]. For TGD individuals living with HIV, viral suppression is an important clinical outcome to reduce morbidity and mortality. It is also key to public health strategies such as U=U (undetectable=untransmittable) aimed at curbing onward transmission of HIV to sexual partners [8]. Multiple individual (eg, demographic), interpersonal (eg, violence), and structural (eg, stigma) factors increase HIV acquisition or transmission risks in TGD people, manifested by decreased rates of PrEP uptake [13] and viral suppression [4,10]. These risk factors are driven by and associated with barriers limiting access to gender-affirming HIV prevention, care, and health services [14-16].

TGD-related HIV disparities are situated alongside adverse mental health conditions (eg, depression, anxiety, and posttraumatic stress disorder), poor psychological functioning, and low health-related quality of life [16-23]. For example, the rates of suicidality among TGD people are devastatingly high, as evidenced by a US national survey of more than 27,000 TGD adults, which found that 40% reported one or more suicide attempts in their lifetime [24]. Behavioral health conditions

adversely affect HIV prevention and care outcomes in TGD people [4,16]. In a 3-year prospective study of TGD women in New York, depressive distress predicted incident HIV or sexually transmitted infection (STI) [25]. In young TGD women living with HIV, those meeting the clinical criteria for depression had an increased probability of having a detectable viral load than those without depression [26]. Histories of psychosocial distress in TGD men are associated with self-reported STI diagnoses, a higher number of sexual partners, and condomless anal or vaginal sex [27,28]. Addressing TGD people's mental health needs and improving psychological functioning are vital components of HIV prevention and treatment interventions [16,29].

Medical gender affirmation therapies—hormones and surgical interventions—are medically necessary treatments shown to improve psychological functioning and quality of life for TGD adults [17,30-37]. It is unknown whether these interventions improve HIV-related outcomes over time in adult TGD patients with diverse gender identities [38]. This is because studies providing the best evidence of medical gender affirmation's clinical effectiveness do not examine outcomes along the HIV prevention continuum (eg, PrEP uptake and adherence) and the HIV care continuum (eg, viral suppression). Integrating medical gender affirmation with HIV prevention and care services may improve HIV-related outcomes for TGD people [29]. Clinical data on barriers and facilitators of medical gender affirmation and unmet needs of TGD people are also lacking. Studies characterizing medical gender affirmation in TGD people by age, race, ethnicity, gender identity, and HIV serostatus are lacking but are paramount to guide health care services and provide patient-centered clinical care [39]. This study will fill these gaps in evidence.

Objectives

The specific aims of this study are to (1) evaluate whether medical gender affirmation improves HIV prevention and care outcomes over 12 months of follow-up, accounting for individual, interpersonal, and structural factors; (2) examine whether medical gender affirmation predicts 12-month prospective improvements in psychological functioning and health-related quality of life (HRQL) in TGD patients initiating

hormone therapy adjusting for individual, interpersonal, and structural factors; and (3) characterize patient satisfaction with medical gender affirmation received, unmet needs and future desires, and barriers and facilitators of medical gender affirmation by age, race, ethnicity, gender identity, and HIV serostatus.

Rationale

Lack of requisite knowledge concerning medical gender affirmation and HIV prevention and care outcomes impede the design, implementation, evaluation, and funding of health care and service delivery models that may reduce HIV disparities for TGD people. Patient-centered care must address and foreground those health issues important to TGD patients. Medical gender affirmation, such as access to and initiation of hormones, is a critical health concern for many TGD patients [40,41]. The delivery of medical gender affirmation in primary care may promote engagement with HIV prevention and care services for TGD people and improve psychological functioning and quality of life. Knowledge obtained from this first-of-its-kind study will inform the delivery of health care responsive to the specific concerns of TGD communities and lead to informed HIV-response efforts for TGD patients, a vulnerable health disparities population for whom clinical effectiveness research is urgently needed. This project will have a national impact on delivering medical gender affirmation in primary care and on intervention models to address HIV and related health disparities for TGD patients.

Methods

Overview

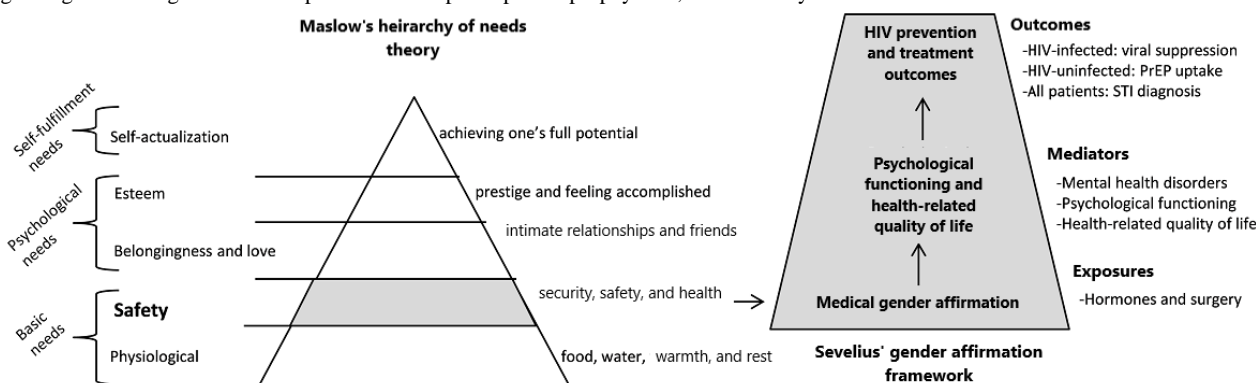
The LEGACY study is being conducted at The Fenway Institute at Fenway Health in Boston, Massachusetts, and Callen-Lorde Community Health Center in New York, New York, 2 federally qualified community health centers with long histories of providing culturally responsive and affirming health care for sexual and gender minority people, including TGD adults [42]. Fenway Health and Callen-Lorde were selected as sites because each has a large medical panel of unduplicated adult TGD patients. The Brigham and Women’s Hospital is the prime

administrative site. All study procedures are approved by the Fenway Health Institutional Review Board (IRB; FWA00000145), which provides single IRB review for this study. All study data are managed by the Fenway Health data informatics team (NCT03595956).

Conceptual Framework: A Biopsychosocial Model of Gender Affirmation and Hierarchy of Needs

This study applies a biopsychosocial model wherein biological, psychological, and social factors are expected to shape health outcomes [43,44]. Within this model, we draw on 2 conceptual frameworks (Figure 1). First, the Model of Gender Affirmation by Sevelius [45] conceptualizes that being affirmed in one’s gender influences psychological functioning and health behaviors (eg, HIV risk behaviors) for TGD people. A high need for gender affirmation and low access to gender affirmation are theorized to fuel poor HIV-related outcomes. Within a biopsychosocial model, it is also possible that hormonal and other system changes accompanying medical gender affirmation exert biological or clinical influences on psychosocial functioning. Second, the hierarchy of needs theory by Maslow [46,47] describes the pattern of motivations that humans generally move through to meet their needs. The theory suggests that at any given time, a certain need *dominates*. The most basic needs (ie, security, safety, and health) must be met before the individual will strongly desire (or focus motivation on) the higher-level needs (ie, belongingness and love, esteem, and self-actualization). Integrating the gender affirmation and hierarchy of needs frameworks, gender affirmation—social, psychological, medical, and legal [48]—takes precedence in the hierarchy of needs for TGD people, given that it pertains to security, safety, and health. Medical gender affirmation, for those TGD people who seek it, is a *dominating* health need that, once met, facilitates TGD patients’ abilities to address other health issues, such as HIV prevention and treatment. In this study, medical gender affirmation (exposure) is the hypothesized driving factor in improving TGD patients’ psychological functioning and HRQL (mediators), thereby increasing TGD individuals’ capacity to become engaged in HIV prevention and care (outcomes).

Figure 1. LEGACY cohort: the biopsychosocial model of gender affirmation and the hierarchy of needs in HIV prevention and treatment outcomes among transgender and gender diverse patients. PrEP: pre-exposure prophylaxis; STI: sexually transmitted infection.



Formative Research: Patient Focus Groups

Formative in-person focus groups were conducted with TGD patients to inform the assembly of and data capture for the cohort. In total, 2 focus groups were conducted at Fenway Health and 2 were conducted at Callen-Lorde. Each group was facilitated by 2 TGD staff members using a semistructured interview guide to gather input on study activities and procedures. A total of 28 people participated in the focus groups. Focus groups were transcribed verbatim, and transcripts were thematically coded by 2 independent analysts using a constant comparative method [49].

Community and Scientific Advisory Boards

A community advisory board (CAB) and a scientific advisory board (SAB) are actively engaged with the research team and provide input on all aspects of the study, including feasibility and acceptability of study procedures. The CAB comprises 7 individuals who identify as TGD or nonbinary people and who advise on keeping the study procedures community centered. The SAB comprises 7 individuals who are researchers and/or medical providers with expertise in transgender health and research methodologies. Each board meets at least twice per year to monitor study progress, troubleshoot challenges, and ensure the achievement of study aims. The SAB also acts as the data safety monitoring board for the study. Members are compensated for their time.

Research Support Coalitions

At each study site, staff engagement is ensured through a research support coalition (RSC). The RSC is in place to represent the voice of staff from within partnering organizations. The RSC is separate from the CAB and SAB so that organizational personnel have the space to bring a staff perspective to project implementation, including feedback on proposed and implemented study activities. The RSC comprises 4 to 6 professional staff members from each partnering site. It includes administrators, clinicians, nurses, HIV prevention staff, and other support staff (eg, peer health navigators and case managers).

Study Design

This longitudinal study comprised a multisite clinic-based cohort of adult TGD patients from Fenway Health and Callen-Lorde. Eligibility criteria for the LEGACY cohort was as follows: (1) aged 18 years or older (verified in the electronic health record [EHR]), (2) having a gender identity different from their sex assigned at birth (verified via a two-step method cross-categorizing natal sex and gender identity reported on patient registration and/or ICD-10 code of F64.0-9) [50,51], (3) being a current or new primary care patient at Fenway Health or Callen-Lorde (defined as those who had a medical visit within the past 12 months), and (4) having a signed patient consent form on file and no research exclusion documented in their patient chart. Patients' biobehavioral data were collected from multiple sources (Table 1).

Table 1. LEGACY cohort: data sources.

Biobehavioral data collected	Patient	EHR ^a	Biomarker
Primary outcomes: HIVPC^b and HIVCC^c			
HIV-infected patients: viral suppression	— ^d	+ ^e	● ^f
HIV-uninfected patients: PrEP ^g uptake	—	+	●
All patients: STI ^h diagnosis (chlamydia and gonorrhea)	X ⁱ	+	●
Exploratory outcome: HIVPC and HIVCC			
HIV-uninfected patients: HIV incidence	—	+	●
Descriptive variables: HIVPC and HIVCC			
HIV-infected patients			
Initiation of ART ^j and adherence to ART	X	+	—
Retention in care	—	+	—
CD4 count	—	+	●
History of opportunistic infections	—	+	—
HIV-uninfected patients			
PrEP indication	X	+	—
PrEP adherence	X	+	—
All patients			
HIV transmission risk behaviors	X	+	—
Exposures: medical gender affirmation			
Primary objective exposure			
Hormones and surgery	X	+	—
Subjective exposure			
Patient satisfaction	X	—	—
Descriptive variables			
Hormones: regimens and experiences	X	+	●
Surgery types and experiences	X	+	—
Street hormones and silicone use	X	+	—
Anatomy inventory	—	+	—
Mediators: mental health disorders, psychological distress, and quality of life			
Mental health and psychiatric diagnoses	X	+	—
Psychological distress	X	+	—
Health-related quality of life	X	—	—
Covariates and confounders: individual, interpersonal, and structural			
Individual			
Demographics and TGD ^k history	X	+	—
Mental health care and medication utilization	X	+	●
Substance use behavior or disorder	X	+	—
Interpersonal			
Transgender integration or adaptation	X	—	—
Violence victimization	X	+	—
Gender of sexual partners	X	+	—
Structural			

Biobehavioral data collected	Patient	EHR ^a	Biomarker
Sex work, housing, and incarceration or jail	X	+	—
Stigma and discrimination	X	—	—

^aEHR: electronic health record.

^bHIVPC: HIV prevention continuum.

^cHIVCC: HIV care continuum.

^dData not collected from that source.

^eElectronic health record data every 3 months.

^fBiomarker or laboratory data.

^gPrEP: pre-exposure prophylaxis.

^hSTI: sexually transmitted infection.

ⁱPatient self-reported survey every 6 months.

^jART: antiretroviral therapy.

^kTGD: transgender and gender diverse.

Study Recruitment and Cohort Enrollment Procedures

The IRB granted a waiver of written consent to allow automatic enrollment of all existing and new TGD adult patients at Fenway Health and Callen-Lorde, who meet the study's eligibility criteria, into the LEGACY research data warehouse (RDW). Deidentified EHRs data (eg, provider-documented diagnoses, biomarker and laboratory data, and pharmacy records) and computerized self-administered patient-reported outcomes (PRO) captured as part of routine care (eg, screening for smoking, depression, and violence) are extracted from the EHR every 6 months. All patients identified as eligible and enrolled in the LEGACY RDW are approached, either in-person at clinic sites with provider permission or via secure email, and asked to complete an additional LEGACY survey at 3 time points over 12 months (baseline, 6 months, and 12 months) and complete optional HIV and STI testing as part of their routine patient care. For HIV and STI testing, a trained phlebotomist at a partner's lab collected blood for HIV-1/2 antigen and antibodies (fourth generation; >99.7% sensitivity and 100% specificity) and for syphilis (rapid plasma reagin and treponema pallidum particle agglutination confirmatory) testing. Urine, vaginal, and anorectal swabs will be provider- or self-collected (depending on participant preference) to test for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* via the APTIMA COMBO 2 Assay (Gen-Probe; >95.2% sensitivity and >96.8% specificity). Participants must be able to read and understand English or Spanish and be willing and able to provide informed consent to participate in the additional survey. Initial eligibility is assessed via the EHR; patients are asked to verify their eligibility before consenting to the survey.

The electronic informed consent form (eICF) for the survey is programmed into REDCap (Research Electronic Data Capture) and is the second form of the electronic survey, preceded only by an eligibility confirmation form. The eICF describes and addresses all study procedures, including confidentiality and privacy, information about potential risks, discomforts and benefits of participation, and information regarding members of the research team to contact for further questions. It also states that participation is voluntary, that participants may decide not to take part or withdraw from the study at any time without

penalty or loss of any benefits to which they might otherwise be entitled, and that study participation is in no way related to being able to access or continue receiving care or services at Fenway Health or Callen-Lorde. Participants are provided with contact information for study staff and are encouraged to call or speak with a staff member if they have any questions before consenting. If a participant agrees to join the study voluntarily, they are asked to consent to the following by checking the applicable boxes: (1) the survey, (2) optional HIV testing, and (3) optional STI testing. Participants who do not consent to optional HIV and/or STI testing are still provided the option to complete the survey.

Staff at both sites aim for patients' consent to LEGACY RDW for survey administration while they are onsite for medical visits. Patients who are not reached this way and are instead contacted via secure email receive a message with information regarding the study and a unique survey link to a screener and consent form. Only eligible patients who provide informed consent are redirected to the survey questions. Survey links expire 14 days after a patient's consent to participate during a medical visit. For patients who provide consent via their web-based unique survey link, the survey link expires 14 days after the secure email was sent. Patients are given the option to begin surveys at their medical visits and continue them remotely on the web should they be unable to complete the survey during their visit; however, surveys must be completed before their 2-week expiration date. If a survey is incomplete, survey progress is saved automatically during a patient's visit, and a unique survey link is emailed to them to bring them to the last saved point in their survey. In addition, patients have the option of saving their progress on all remote surveys and continuing where they left off at their convenience; however, all surveys must be completed before their 2-week expiration date.

Patients enrolled in the LEGACY RDW or who complete the additional brief surveys integrated with routine patient care are not individually compensated. Patients who complete the surveys have the option to be entered into a raffle to win an Amazon gift card. At the end of the survey, patients are asked to indicate if they consent to be contacted either via the phone number or email (or both) listed on their patient record for the raffle. At each site, 2 winners are selected per month per

assessment point. For example, of those who complete a baseline survey in the month of February, 2 are randomly selected from each site for a gift card. As surveys are completed, they are assigned a consecutive number in REDCap; a web-based random number generator is used to randomly select a number from the list of completed surveys within the specified month for the raffle. The winner is contacted via their preferred method and given 1 week to respond and/or claim their gift card.

Patient Self-Reported Outcome Measures

The PRO measures in the LEGACY surveys are aligned with the study aims. Wherever possible, validated self-report measures from previous TGD research are asked to ensure cultural appropriacy and comparability across studies. Measures have been drawn from probability and nonprobability sample studies, including the US Transgender Population Health Survey [52], National Transgender Discrimination Survey [53], the 2015 US Transgender Survey [24], LITE Cohort [54], Project LifeSkills [55], Project VOICE [20,56], and TransMasculine Sexual Health Study [57].

Sociodemographic factors such as age, gender identity, sex assigned at birth, sexual orientation, racial or ethnic identity, employment, education, and income are queried. Sexual health measures include STI screening history and diagnoses [57], HIV testing history [58], HIV care cascade engagement for patients with HIV (antiretroviral therapy initiation and adherence using the Visual Analogue Scale) [59], HIV prevention cascade engagement for patients without HIV (PrEP indication, awareness, uptake, adherence, persistence, and side effects) [54], HIV transmission risk behaviors, and sexual partnerships including condomless sex and gender of sexual partners [60]. Medical gender affirmation assessment includes hormone use (age of initiation and access, regimens, side effects and experiences, and patient satisfaction), surgical procedures (current uptake, future desires for procedures, experiences and medical complications, and patient satisfaction), and medical gender affirmation outside of medical contexts (street hormones and silicone use).

Assessment of psychological factors includes suicidality and experiences of hospitalization for mental health [61], psychological distress by the validated Patient Health Questionnaire-4 [62] and Kessler-6 [63], gender dysphoria by a brief screening measure designed to maximize patient-centeredness [64], HRQL by the EQ-5D-5L [65], substance use and misuse by the Alcohol Use Disorders Identification Test-Concise [66] and the Drug Abuse Screening Test-10 [67], transgender integration or adaptation [68], violence victimization in childhood and adulthood [20], and stigma and discrimination by a modified version of the Everyday Discrimination Scale [69]. Structural vulnerabilities such as sex work, housing, and jail and incarceration experiences and barriers to legal gender affirmation (eg, changing name and gender marker on identification) were also measured [52,54].

Optional HIV and STI Testing

Biological specimens are collected for HIV and/or bacterial STI testing from relevant anatomical sites of participants who have clinical indications, as determined by their medical provider.

Participants for whom HIV and/or STI testing are not clinically indicated but who request and consent to the optional additional cohort testing have a flag added to their patient chart by research staff, alerting the provider to order these tests. All specimens are sent to the clinics' site labs for analysis, per medical department procedures. Participants complete these tests in concert with their routine lab work. Test results are extracted from their patient chart.

Study Retention

We expect to retain approximately 85% of those who consent to additional procedures (electronic survey and HIV or STI testing) across 12 months of follow-up. Data informatics personnel and research assistants at each site work collaboratively to track cohort participants and contact participants when it is time to take their follow-up surveys. Study activities are synced with routine clinical care as much as possible to minimize participant burden. Study retention and participant engagement activities are ongoing. Participants can opt-in to receive study updates in the form of a newsletter. Study updates occur via email approximately 3 times over 12 months. The email contains general updates about the study (eg, how many have enrolled to date, fun facts about the cohort, and other study milestones) and infographics with deidentified preliminary demographic and other data. The email is not sent to those who have declined to receive study updates. The purpose of the newsletter is to provide progress updates to participants and promote participant engagement, including evoking feelings of being *part of* and actively contributing to the project and the study team at each site. The newsletter emails are sent via a health insurance portability and accountability act (HIPAA)-compliant mass-messaging platform.

LEGACY RDW Procedures

The LEGACY RDW is a HIPAA limited data set. The HIPAA limited data set may contain extensive clinical information on study participants but limits patient identifiers and other unique characteristics to preclude the possibility that the patient could be identified using data transmitted to the RDW.

Quality Assurance

The LEGACY RDW employs various data resources to aid in the quality, maintenance, and security of patient data. Data resources are maintained, regularly monitored, evaluated, and updated. For survey data, quality assurance (QA) begins in the recruitment process. Recruitment scripts screen health record data to determine prospective patients' eligibility before outreach. Research assistants review the outputs for these scripts and report any suspected ineligible patients so that necessary updates may be applied. Patients deemed eligible by the recruitment scripts are then offered a screener where they self-report eligibility criteria before the consent process. The survey uses restricted input options and pathing logic to promote data accuracy and completeness. In some cases, key survey data points are crosstabulated and reviewed for any erroneous response patterns not identified by the survey's built-in QA tools. QA for the LEGACY RDW includes running scripts across data tables to check for errors, such as duplicated rows and orphaned records. The LEGACY RDW relies on the QA

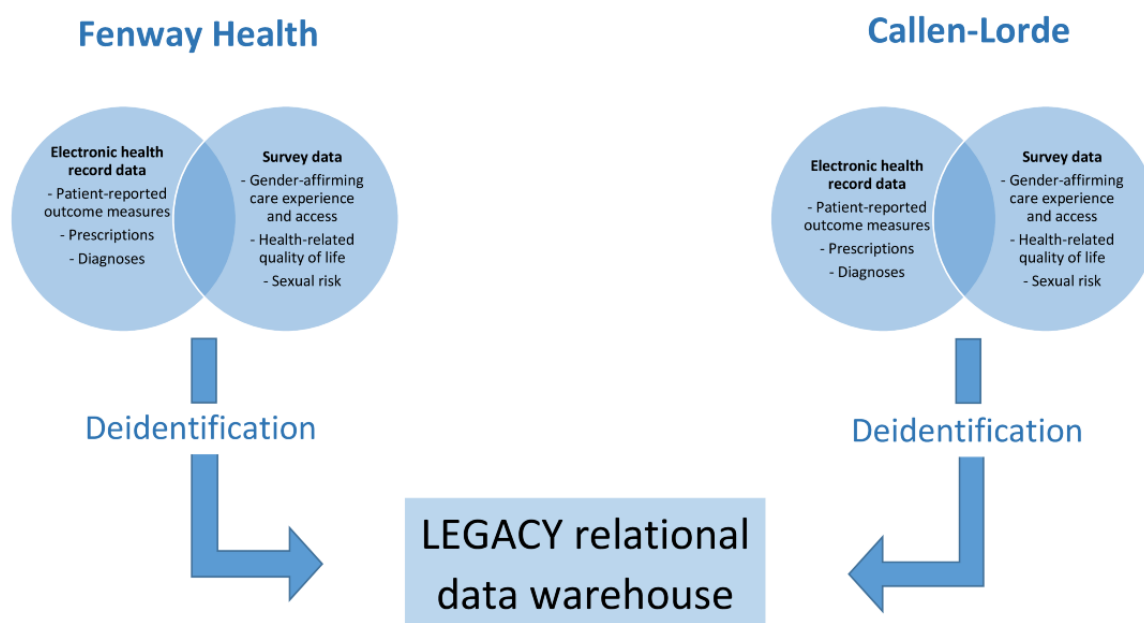
processes managed by the native EHR systems for measures of completeness and accuracy. Staff at both sites regularly maintain extraction, transformation, and loading scripts to ensure they are congruent with the most recent version of their native EHR systems.

Data Sources

The LEGACY RDW integrates outpatient, health center, and patient self-reported survey data for TGD patients into a single data management system (Figure 2). The comprehensive EHR systems at Fenway Health (Centricity Practice Solutions, athenahealth product) and Callen-Lorde (NextGen Ambulatory EHR, version 5.9/8.4) include patient demographics; registration and appointments; claims; encounter or problem list diagnoses; vital signs; lab orders and results; prescriptions; procedure or referral orders; provider notes; PROs conducted as part of

routine clinical care (eg, screening for smoking, depression, and violence); imaging services; behavioral health data; dental care data; and information on patients with acute, chronic, or episodic conditions requiring special attention. These comprehensive outpatient data sources capture information on a broad range of primary care services, the most common services used by US patients. These data sources also include specialty care services to inform research questions regarding medical gender affirmation, HIV prevention, and HIV care. The LEGACY RDW is designed to enhance the breadth of the horizontal outpatient data sets by adding vertical depth with self-reported survey data from patients. Integrating electronic patient-reported survey data allows gathering of information that is not currently captured in the patient record (eg, incarceration, desires for gender-affirming procedures, and experiences in health care) to achieve the main study aims.

Figure 2. LEGACY cohort: study flow diagram. EHR: electronic health record.



EHR Data Submission Procedures

A data usage agreement (DUA) was established before Callen-Lorde shares any identifying information regarding their patients with Fenway Health.

Data come directly from the partnering site. Partners have access to a secure FTP (file transfer protocol) server within Fenway Health's firewall to transfer the limited data set. Data partners have their own user IDs and passwords, and each data partner's data set is segregated into individual directories. A waiver of consent and authorization specifically for patient data coming from partners' EHRs was granted because it is not practicable to go back and obtain consent and authorization from the over 5000 patients whose health records make up the RDW.

LEGACY Surveys

Self-report survey data for TGD patients are collected using REDCap [70,71]. REDCap is a secure web-based app validated to ensure HIPAA-compliant data collection. Survey data collected through REDCap are stored on a secure Fenway Health

server before being extracted and transferred into the LEGACY RDW. Consent obtained before survey administration is stored in REDCap, with survey data and transferred into the LEGACY RDW along with survey responses.

Although the survey is hosted on Fenway Health's servers, each research site manages survey administration for their own patients. Patient email addresses are maintained within their REDCap study records to enable the emailing of surveys to patients. To permit Callen-Lorde staff to enter their patients' email addresses into Fenway Health's REDCap server, both parties signed a DUA that covers sharing Callen-Lorde's patients' email addresses with database administrators at Fenway Health. Callen-Lorde was given their own REDCap project and log-in credentials for managing their surveys. Database administrators at Fenway created REDCap user access groups that restricted other Fenway Health staff from accessing Callen-Lorde's REDCap records and restricted Callen-Lorde staff from accessing Fenway Health REDCap records. Fenway Health database administrators are the only staff members with access to REDCap study records for both sites.

Fenway Health uses patient medical record numbers (MRNs) as the primary identifier for their patients' REDCap study records. Patient MRNs are replaced with LEGACY study IDs before the survey data are imported into the LEGACY RDW. Callen-Lorde preassigns LEGACY study IDs to their patients and uses the study ID as the primary identifier in their patients' REDCap study records. Callen-Lorde's study staff maintains their own link file connecting their patients' study records back to their MRNs outside of REDCap. Callen-Lorde's patients' MRNs are never entered into the REDCap study records.

Security and Confidentiality

The LEGACY RDW is stored within Fenway Health's secure firewall on a server requiring log-in credentials from authorized Fenway Health staff. Only the Fenway Health database administrators assigned to the project have direct access to the full RDW. All other study personnel who require access to any data elements are given access to the appropriate data elements according to their role and need. In preliminary steps, data structures are designed to separate personal identifiers from other critical data, further enhancing protection. All partnering organizations meet or exceed the requirements for patient data safety established in the federal HIPAA guidelines.

Confidentiality Agreements

All persons employed by Fenway Health and Callen-Lorde sign a confidentiality agreement. Fenway Health has an excellent record of using EHR data for research without breach of

confidentiality. No individual-identifying data will be published or released, and data will be summarized and presented in public forums only as aggregate measures or as results from statistical analyses.

Statistical Considerations

The study outcomes are viral suppression (for TGD patients living with HIV); PrEP uptake (for TGD patients not living with HIV); and incident syphilis, gonorrhea, and chlamydia diagnoses by anatomical site (for all patients, irrespective of HIV status). The primary exposure is medical gender affirmation (hormones and surgery).

Sample Size

We assumed $\alpha=.05$ (two-tailed; type I error rate) and $\beta=.20$ (type II error rate) for sample size estimation. The primary power analysis is based on virologic suppression (<200 copies per ml: yes or no) for TGD patients living with HIV (Tables 2 and 3). We hypothesize that medical gender affirmation (hormones and surgery vs none) will increase the proportion of HIV-infected TGD patients achieving viral suppression across follow-up. There is substantial variability in viral suppression rates among TGD people (eg, 50%-81%) [10-12,72,73]. A 25% increase in the proportion of TGD patients achieving viral suppression (moderate treatment effect), from 51% at baseline to 76% at follow-up, will require a minimum sample size of 182 patients living with HIV. Analyses of PrEP uptake and STI diagnoses are equally well-powered.

Table 2. LEGACY cohort: parameter estimates used in sample size estimation for viral suppression, pre-exposure prophylaxis uptake, and sexually transmitted infection diagnosis.

Outcome variable	Parameter estimate
Viral suppression	
P ₀ ^a	0.51
P ₁ ^b	0.76
Odds ratio ^c	3.04
Risk ratio ^d	1.49
PrEP^e uptake	
P ₀	0.011
P ₁	0.048
Odds ratio	4.53
Risk ratio	4.36
STI^f diagnosis	
P ₀	0.052
P ₁	0.210
Odds ratio	4.85
Risk ratio	4.04

^aP₀: risk in group 0 (baseline risk).

^bP₁: risk in group 1 (exposed).

^cOdds ratio: $((P_1/(1-P_1))/(P_0/(1-P_0)))$.

^dRisk ratio: (P₁ to P₀).

^ePrEP: pre-exposure prophylaxis.

^fSTI: sexually transmitted infection.

Table 3. LEGACY cohort: sample size estimation for viral suppression, pre-exposure prophylaxis uptake, and sexually transmitted infection diagnosis.

Outcome variable	Outcome+	Outcome–	Total
Viral suppression			
Group 1	113	36	149
Group 0	17	16	33
Total	130	52	182
PrEP^a uptake			
Group 1	49	967	1016
Group 0	2	221	223
Total	51	1188	1239
STI^b diagnosis			
Group 1	45	168	213
Group 0	2	45	47
Total	47	213	260

^aPrEP: pre-exposure prophylaxis.

^bSTI: sexually transmitted infection.

Data Analysis

Descriptive statistics (eg, frequencies, means, and standard deviations) will be obtained to summarize the variables. Bivariate tests (t tests or χ^2) will examine differences by site. Subsequent analyses will use appropriate statistical procedures to adjust for site differences if necessary. Bivariate tests (t tests or χ^2) will examine medical gender affirmation by HIV outcomes of interest, followed by multivariable regression models. Analyses will use SAS software with two-tailed tests and an alpha .05-level of significance.

Aim 1 analyses will involve descriptive statistics to characterize medical gender affirmation exposures and HIV prevention continuum (HIVPC) and HIV care continuum (HIVCC) outcomes at baseline and each follow-up over 12 months. We will model longitudinal HIV-related outcome trajectories as a function of medical gender affirmation using generalized estimating equations [74]. Models will be adjusted for individual, interpersonal, and structural covariates and confounders. Moderators (eg, age, race, and gender identity) will be tested to identify TGD patients at the highest and lowest risk of adverse outcomes. For example, we will evaluate whether racial or ethnic self-identification (people of color vs White) is an effect modifier of hormones and viral suppression (ie, whether there is heterogeneity in treatment effects by race). Analyses will be appropriately stratified for heterogeneous treatment effects.

In aim 2, we will longitudinally model within-person changes in mental health diagnoses and response to standardized behavioral assessments from baseline (prehormones) to 12-months (aim 2) among TGD patients prospectively initiating hormone therapy at cohort entry. Mediation models will test whether changes in mental health explain the effect of medical gender affirmation on improved HIVPC or HIVCC outcomes.

Aim 3 analyses will entail descriptive statistics to characterize patient satisfaction with medical gender affirmation received, unmet needs and future desires for medical gender affirmation, and barriers and facilitators of medical gender affirmation.

Missing data can create significant problems in the analysis or interpretation of longitudinal data. Statistical summaries will be used to describe the missing data. We will assess patterns of missing data between or within follow-ups [75-77], comparing patients in care with those who drop out of care. We will use modern missing data techniques as appropriate, such as multiple imputation [78,79]. The impact of unmeasured confounders will be evaluated via sensitivity analyses [80]. We will also test for heterogeneity of treatment effects in medical gender affirmation and HIVPC or HIVCC outcomes, consistent with the PCORI (Patient-Centered Outcomes Research Institute) methodology standards.

Fenway Health is the lead for data analysis and the creation of analytic data sets. This group is staffed by doctoral and master's level biostatisticians who have extensive experience analyzing health outcomes using various statistical approaches. For LEGACY, they will be the primary resource for statistical consulting on any future grant proposals, concept sheets, study design, statistical analyses, and manuscript preparation. A

delineated concept proposal process is in place to facilitate collaborations or data requests for the cohort. Any requests for access to the analysis data sets require previous approval from the principal investigator and applicable oversight bodies such as PCORI or the Fenway IRB.

Results

Formative Research Findings: Focus Groups

The contract began in April 2018. The Fenway Health IRB approved the formative focus group procedures in June 2018. All formative focus groups were conducted between August and October 2018. Among the 28 focus group participants, the mean age was 34 years (range 18-66 years); 13 identified as female, 12 were identified as male, and 3 identified as nonbinary; 12 were White, 5 Black or African American, 5 multiracial, 3 Asian or Pacific Islander, and 3 other race; and 8 identified as Hispanic or Latinx.

Several themes emerged from focus groups that informed cohort protocol and procedures:

1. Study population: participants strongly advocated for the inclusion of gender nonbinary patients in the research. They suggested that the team intentionally outreach to and engage TGD communities for inclusion and participation.
2. Research topics: participants felt that the reinforcement of negative transgender narratives was the main cause of research fatigue in the TGD community. Thus, they wanted the study to ask TGD patients about resiliencies and strengths, in addition to disparities and deficits.
3. Integration of clinical care and research: participants liked how the study was being integrated into their primary care, making participating efficient and low barrier. Most participants were comfortable with their medical records being accessed for the purposes of the study. Participants felt specimen collection for HIV or STIs should be optional and that the uses of the specimens should be clearly and transparently explained through an informed consent process separate from that of the survey.
4. Incentives for participation: there was a range of opinions regarding financial compensation and incentives. In 2 of the focus groups, participants strongly felt that the survey portion of the study should be remunerated, citing financial disparities facing TGD populations. Other groups felt that financial compensation was not required. These participants felt that the survey content alone would keep participants engaged and that the mission of the project was compensation enough.
5. Dissemination activities: focus group participants expressed the importance of disseminating research findings back to the community. They wanted results to be shared throughout the entire research process, rather than waiting until the end to hear about it or to not hear about it at all.

Cohort Recruitment, Enrollment, and Retention

The longitudinal cohort was approved by the IRB in January 2019. Prospective cohort enrollment began at Fenway Health in February 2019 and at Callen-Lorde in August 2019. Enrollment will continue through August 2020. As of April

2020, 7821 patients have been enrolled in the LEGACY RDW and 1756 have completed the additional baseline LEGACY survey. The baseline characteristics of the TGD patients in the RDW and survey are shown in [Tables 4](#) and [5](#), respectively. Recruitment strategies that have demonstrated success include posting of study flyers in exam rooms and patient waiting areas (see [Figure 3](#) for an example), educating providers about the study to facilitate successful patient referrals and linkages to

the research (eg, presenting on the study to medical departments), and building a study identity that links to and is integrated with each clinical site's transgender health program and services. Ongoing retention efforts consist of frequent reminder emails about upcoming survey participation and dissemination of study e-newsletters, which contain preliminary findings from the cohort to date (see [Figure 4](#) for an example).

Table 4. Baseline electronic health record data for transgender and nonbinary adult patients (N=7821).

Sociodemographics	Values ^a , n (%)
Age (years)	
18-24	2165 (27.68)
25-29	2117 (27.07)
30-39	2193 (28.04)
40-49	705 (9.01)
50-59	404 (5.17)
≥60	237 (3.03)
Gender identity	
Female	2900 (37.08)
Male	2643 (33.79)
Genderqueer	1700 (21.74)
Missing	578 (7.39)
Sex assigned at birth	
Female	4064 (51.96)
Male	3649 (46.66)
Missing	108 (1.38)
Race	
American Indian or Alaska Native	74 (0.95)
Asian	378 (4.83)
Black or African American	1070 (13.68)
Multiracial	475 (6.07)
Pacific Islander	61 (0.79)
White	4717 (60.31)
Missing	1046 (13.37)
Ethnicity	
Hispanic or Latinx	1152 (14.73)
Non-Hispanic or Latinx	5093 (65.12)
Missing	1576 (20.15)
Gender affirmation	
Current hormone prescription	
Yes	6855 (87.65)
No	966 (12.35)
HIV and STIs^b	
HIV-positive serostatus	
Yes	421 (5.38)
No	7400 (94.62)
Current PrEP^c prescription	
Yes	727 (9.30)
No	7094 (90.70)
Previous STI diagnosis (non-HIV)	
Yes	3257 (41.64)

Sociodemographics	Values ^a , n (%)
No	4564 (58.36)

^aData from transgender and gender diverse patients with a primary care medical visit between January 7, 2018, and February 29, 2020.

^bSTI: sexually transmitted disease.

^cPrEP: pre-exposure prophylaxis.

Table 5. Baseline patient-reported survey data for transgender and nonbinary adult patients (n=1756). Data from transgender and gender diverse patients with a primary care medical visit between January 7, 2018, and February 29, 2020.

Sociodemographics	Values, n (%)
Age (years; n=1756)	
18-24	582 (33.14)
25-29	440 (25.06)
30-39	476 (27.11)
40-71	253 (14.41)
Missing	5 (0.28)
Gender identity (n=1756)	
Trans man	743 (42.31)
Trans woman	504 (28.70)
Genderqueer or nonbinary AFAB ^a	382 (21.75)
Genderqueer or nonbinary AMAB ^b	95 (5.41)
Missing	32 (1.83)
Sex assigned at birth (n=1756)	
Female	1130 (64.35)
Male	610 (34.74)
Missing	16 (0.91)
Race (n=1756)^c	
American Indian or Alaska Native	0 (0.0)
Asian	52 (2.96)
Black or African American	76 (4.33)
Latinx	87 (4.95)
Multiracial	245 (13.95)
Native Hawaiian or Other Pacific Islander	11 (0.63)
White	1253 (71.36)
Another race	17 (0.97)
Missing	15 (0.85)
Ethnicity (n=1756)^c	
Hispanic or Latinx	175 (9.97)
Non-Hispanic or Latinx	1566 (89.18)
Missing	15 (0.85)
Sexual orientation (n=1756)	
Asexual	72 (4.10)
Bisexual	286 (16.29)
Gay	126 (7.18)
Lesbian	179 (10.19)
Pansexual	234 (13.33)
Queer	544 (30.98)
Questioning or unsure	54 (3.07)
Straight or heterosexual	211 (12.01)
Another sexual orientation	34 (1.94)

Sociodemographics	Values, n (%)
Missing	16 (0.91)
Educational attainment (n=1756)	
High school diploma or less	193 (10.99)
Associate's degree, vocational or technical school, or some college	529 (30.12)
4-year degree	633 (36.05)
Graduate degree	282 (16.06)
Another level of education	17 (0.97)
Missing	102 (5.81)
Type of health insurance (n=1756)	
None	51 (2.91)
Public	446 (25.40)
Private	1182 (67.31)
Missing	77 (4.38)
Lifetime hormone use (n=1756)	
Taken hormones	1456 (82.91)
Have not taken hormones but interested in taking them	234 (13.33)
Have not taken hormones and not interested in taking them	62 (3.53)
Missing	4 (0.23)
Current hormone use (n=1456)	
Yes	1399 (96.09)
No	57 (3.91)
History of gender-affirming surgeries or procedures (n=1756)	
Yes	1009 (57.46)
No	746 (42.48)
Missing	1 (0.06)
Gender-affirming surgeries or procedures by region (dichotomous; n=1009)	
Any facial or voice procedures	161 (15.96)
Any chest procedures	624 (61.84)
Any abdomen or bottom procedures	305 (30.23)
Heard about pre-exposure prophylaxis for HIV prevention? (n=1756)	
Yes	1395 (79.44)
No	240 (13.67)
I do not know	28 (1.59)
Missing	93 (5.30)
Ever taken pre-exposure prophylaxis? (n=1395)	
Yes	136 (9.75)
No	1255 (89.96)
Missing	4 (0.29)
Ever been tested for HIV? (n=1756)	
Yes	1151 (65.55)
No	409 (23.29)
I do not know	106 (6.04)
Missing	90 (5.12)

Sociodemographics	Values, n (%)
Result of most recent HIV test (n=1151)	
HIV positive	19 (1.65)
HIV negative	1094 (95.05)
Undetermined	7 (0.61)
I do not know	25 (2.17)
Missing	6 (0.52)
Ever had an STI^d test (non-HIV; n=1756)	
Yes	1194 (68.00)
No	372 (21.18)
I do not know	95 (5.41)
Missing	95 (5.41)
Ever tested positive for an STI (non-HIV; n=1194)	
Yes	246 (20.60)
No	926 (77.55)
I do not know	15 (1.26)
Missing	7 (0.59)
Clinically significant depression^e (n=1753)	
Yes	604 (34.46)
No	1149 (65.54)
Clinically significant anxiety^e (n=1753)	
Yes	744 (42.44)
No	1008 (57.50)
Missing	1 (0.06)

^aAFAB: assigned female sex at birth.

^bAMAB: assigned male sex at birth.

^cRace and ethnicity are assessed using a single item. Participants who select only Latinx for their racial or ethnic identity are coded to have a race of Latinx. Any participant who selects Hispanic or Latinx (not mutually exclusive) is coded to have an ethnic identity of Hispanic or Latinx.

^dSTI: sexually transmitted disease.

^eThe frequency of depressive and anxious symptoms experienced over the past 2 weeks is assessed using the Patient Health Questionnaire-4, comprising 4 items with response options ranging from not at all (0) to nearly every day (3). The cutoff for clinically significant depression is a score of >3 summed across the 2 items assessing depressive symptoms (feeling down, depressed, or hopeless and little interest or pleasure in doing things). The cutoff for clinically significant anxiety is a score of >3 summed across the 2 items for anxious symptoms (feeling nervous, anxious, or on edge and not being able to control worrying).

Figure 3. LEGACY cohort: example of study recruitment flyer.



WHAT DO YOU WANT YOUR LEGACY TO BE?

Did you know that Fenway Health and Callen-Lorde serve the largest number of trans and non-binary (TGNB) patients in the country? Combined, Fenway and Callen-Lorde serve almost 10,000 TGNB people. Collectively, our voices have power.

How can we make healthcare for TGNB people even better? Ask TGNB people!

The LEGACY Project is the first community-based transgender cohort study...EVER. We are using health information from the clinic and survey data to see how gender-affirming healthcare affects health outcomes like quality of life, mental health, and sexual health. The LEGACY Project is an opportunity to share your healthcare experiences and inform care for TGNB people nationally. With the information gained in this study, we hope to influence approaches to transgender health across the nation and worldwide.



The LEGACY Project is led, designed, and run by and for TGNB people. Our research team is led by TGNB scientists and experts at both Fenway Health and Callen-Lorde. It's our mission to host a study that represents all of our TGNB patients.

To participate in The LEGACY Project, talk to your medical provider at your next appointment. You can take the survey at your appointment, or it can be emailed to you to complete at a later time. Everyone will take 3 surveys over the course of one year. After you complete each survey, you will be entered into a raffle to win a \$50 gift card!

FENWAY  HEALTH

TFIR-95

Figure 4. LEGACY cohort: example of participant newsletter.

OUR HEALTH. OUR LEGACY.



1,100

PARTICIPANTS ENROLLED
AT FENWAY HEALTH



96% ARE CURRENTLY
ON HORMONES

MEDIAN AGE

Age range 18-71 years, with middle point at 27.



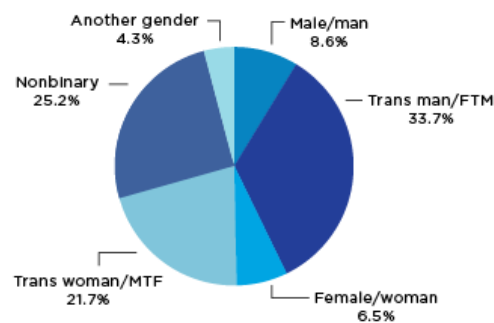
SELF REPORTED CURRENT HEALTH



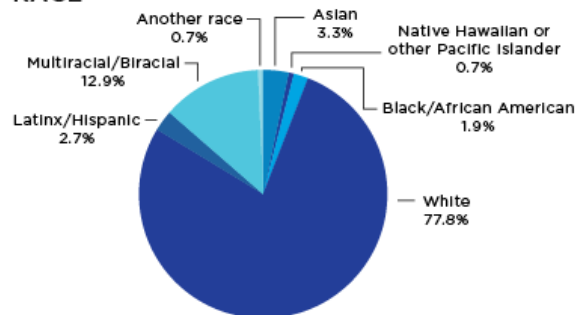
When asked to rate their current health on a scale from 0 to 100 (worst health imaginable to best health imaginable), participants reported a median score of 75.

DATA AS OF DECEMBER 2019

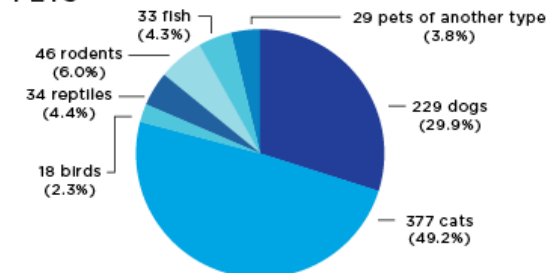
GENDER IDENTITY



RACE



PETS



Discussion

Principal Findings

This study is an unprecedented opportunity to evaluate the impact of medical gender affirmation on HIV-related health among TGD patients, an understudied health disparities population. LEGACY will uniquely contribute to the longitudinal evidence base on medical gender affirmation and

HIV-related health in TGD patients. The comprehensive research methodology links biobehavioral longitudinal data from multiple sources, including EHR, patient self-reported outcomes, and biospecimen testing. Patient-centeredness and scientific rigor are assured through the ongoing engagement of TGD people, including as community members, clinicians, scientists, and site staff.

The LEGACY cohort can serve as a platform for ongoing and new research studies. The common data model used for the

study is flexible and offers the potential to easily build out and enhance the cohort with new research sites and patients in the future to create a large repository. Furthermore, the cohort infrastructure can be leveraged by other research projects, such as case-control studies interested in isolating iatrogenic effects of particular medical gender affirmation exposures, biomedical investigations such as pharmacokinetic studies of drug-hormone interactions, or mixed methods quantitative-qualitative designs to gather in-depth perspectives on health care needs. By characterizing the impact of medical gender affirmation on the lives of TGD patients, findings from the LEGACY cohort will inform evidence-based clinical care for TGD patients, including optimal interventions to improve HIV-related health disparities.

Limitations

Limitations of the study are weaknesses inherent in a clinical cohort that recruits existing and new patients, including *clinic patient bias* and limited generalizability. For example, the cohort is relatively young in terms of age and has lower rates of lacking health insurance than previous research [24], which may challenge the generalizability of findings. Another limitation is the self-selection of participants into treatments (eg, patients

self-select hormones). However, the LEGACY cohort overcomes many of the limitations of other TGD cohorts, namely, lack of racial and ethnic diversity, restriction to TGD patients in gender clinics, and a high number of nonbinary-identified patients.

Dissemination Plans

Patients and stakeholders will be engaged in dissemination activities, both to the scientific community and the TGD communities. CAB, SAB, and RSC members will be given the opportunity to present study findings at relevant conferences and will be involved in the writing of peer-reviewed scientific manuscripts. In addition, the CAB, SAB, and RSC will be responsible for the creation and dissemination of a community report, which will outline the key study findings in lay terms and provide recommendations for community members, patients, and other key stakeholders. Patient and stakeholder partners will be involved in plans to disseminate study findings and to ensure that findings are communicated in understandable, practical, and usable ways that will inform high-quality patient-centered care for TGD people.

Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

CAB: community advisory board
DUA: data usage agreement
EHR: electronic health record
eICF: electronic informed consent form
HIPAA: health insurance portability and accountability act
HIVCC: HIV care continuum
HIVPC: HIV prevention continuum
HRQL: health-related quality of life
IRB: institutional review board
MRN: medical record number
PrEP: pre-exposure prophylaxis
PRO: patient-reported outcome
QA: quality assurance
RDW: research data warehouse
RSC: research support coalition
SAB: scientific advisory board
STI: sexually transmitted infection
TGD: transgender and gender diverse

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Protocol

Improving the Understanding of the Immunopathogenesis of Lymphopenia as a Correlate of SARS-CoV-2 Infection Risk and Disease Progression in African Patients: Protocol for a Cross-sectional Study

Bamidele Abiodun Iwalokun¹, BSc, MSc, PhD; Adesola Olalekan², PhD; Eyitayo Adenipekun², PhD; Olabisi Ojo³, PhD; Senapon Olusola Iwalokun⁴, MBBS; Bamidele Mutiu⁵, MD; Oluseyi Orija⁶, MPH; Richard Adegbola⁷, PhD; Babatunde Salako¹, MD; Oluyemi Akinloye², PhD

¹Nigerian Institute of Medical Research, Lagos, Nigeria

²Department of Medical Laboratory Sciences, Faculty of Basic Medical Science, College of Medicine, University of Lagos, Lagos, Nigeria

³Department of Natural Sciences, Albany State University, Georgia, GA, United States

⁴Lagos State Ministry of Health, Lagos, Nigeria

⁵Department of Medical Microbiology & Parasitology, College of Medicine, Lagos State University, Lagos, Nigeria

⁶Department of Public Health, National University, San Diego, CA, United States

⁷Microbiology Department, Nigerian Institute of Medical Research, Lagos, Nigeria

Corresponding Author:

Bamidele Abiodun Iwalokun, BSc, MSc, PhD

Nigerian Institute of Medical Research

6 Edmund Crescent, Yaba-Lagos

PMB 2013

Lagos, 23401

Nigeria

Phone: 234 08023357646

Email: ba.iwalokun@nimr.ov.ng

Abstract

Background: The COVID-19 pandemic, caused by SARS-CoV-2, continues to impact health systems throughout the world with serious medical challenges being imposed on many African countries like Nigeria. Although emerging studies have identified lymphopenia as a driver of cytokine storm, disease progression, and poor outcomes in infected patients, its immunopathogenesis, as well as environmental and genetic determinants, remain unclear. Understanding the interplay of these determinants in the context of lymphopenia and COVID-19 complications in patients in Africa may help with risk stratification and appropriate deployment of targeted treatment regimens with repurposed drugs to improve prognosis.

Objective: This study is designed to investigate the role of vitamin D status, vasculopathy, apoptotic pathways, and vitamin D receptor (VDR) gene polymorphisms in the immunopathogenesis of lymphopenia among African people infected with SARS-CoV-2.

Methods: This cross-sectional study will enroll 230 participants, categorized as “SARS-CoV-2 negative” (n=69), “COVID-19 mild” (n=32), “hospitalized” (n=92), and “recovered” (n=37), from two health facilities in Lagos, Nigeria. Sociodemographic data, travel history, and information on comorbidities will be obtained from case files and through a pretested, interview-based structured questionnaire. Venous blood samples (5 mL) collected between 8 AM and 10 AM and aliquoted into EDTA (ethylenediaminetetraacetic acid) and plain tubes will be used for complete blood count and CD4 T cell assays to determine lymphopenia (lymphocyte count <1000 cells/ μ L) and CD4 T lymphocyte levels, as well as to measure the concentrations of vitamin D, caspase 3, soluble vascular cell adhesion molecule-1 (sVCAM-1), and soluble Fas ligand (sFasL) using an autoanalyzer, flow cytometry, and ELISA (enzyme-linked immunosorbent assay) techniques. Genomic DNA will be extracted from the buffy coat and used as a template for the amplification of apoptosis-related genes (*Bax*, *Bcl-2*, *BCL2L12*) by polymerase chain reaction (PCR) and genotyping of VDR (Apa1, Fok1, and Bsm1) gene polymorphisms by the PCR restriction fragment length polymorphism method and capillary sequencing. Total RNA will also be extracted, reverse transcribed, and subsequently quantitated by reverse transcription PCR (RT-PCR) to monitor the expression of apoptosis genes in the four participant categories. Data analyses, which

include a test of association between VDR gene polymorphisms and study outcomes (lymphopenia and hypovitaminosis D prevalence, mild/moderate and severe infections) will be performed using the R statistical software. Hardy-Weinberg equilibrium and linkage disequilibrium analyses for the alleles, genotypes, and haplotypes of the genotyped VDR gene will also be carried out.

Results: A total of 45 participants comprising 37 SARS-CoV-2–negative and 8 COVID-19–recovered individuals have been enrolled so far. Their complete blood counts and CD4 T lymphocyte counts have been determined, and their serum samples and genomic DNA and RNA samples have been extracted and stored at –20 °C until further analyses. Other expected outcomes include the prevalence and distribution of lymphopenia and hypovitaminosis D in the control (SARS-CoV-2 negative), confirmed, hospitalized, and recovered SARS-CoV-2–positive participants; association of lymphopenia with CD4 T lymphocyte level, serum vitamin D, sVCAM-1, sFasL, and caspase 3 levels in hospitalized patients with COVID-19; expression levels of apoptosis-related genes among hospitalized participants with COVID-19, and those with lymphopenia compared to those without lymphopenia; and frequency distribution of the alleles, genotypes, and haplotypes of VDR gene polymorphisms in COVID-19–infected participants.

Conclusions: This study will aid in the genotypic and phenotypic stratification of COVID-19–infected patients in Nigeria with and without lymphopenia to enable biomarker discovery and pave the way for the appropriate and timely deployment of patient-centered treatments to improve prognosis.

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KEYWORDS

SARS-COV-2 infection; COVID-19; lymphopenia; immunopathogenesis; Nigeria

Introduction

Background

COVID-19, caused by the novel betacoronavirus SARS-CoV-2, which originated from Wuhan, China, in 2019, has spread to over 200 countries worldwide, infecting thousands of health care workers [1]. COVID-19 continues to impact health systems globally, with serious medical challenges imposed on many African countries such as Nigeria. The disease has contributed to an overwhelming number of hospitalizations of infected patients and rising needs for hospital beds and life-saving equipment [1-3]. COVID-19 incidence is increasing in many African countries due to burgeoning community tertiary transmission rates, which has resulted in a rising number of deaths and challenges in diagnosis and treatment [4]. As of May 12, 2020, in the African continent, a total of 69,126 cases and 2386 deaths, representing a case fatality rate of 3.5%, have been reported [5]. Nigeria currently ranks as the fourth most affected country in Africa, with 4787 cases, 158 deaths, and a case fatality rate of 3.3%, as of May 12, 2020. These indices are higher than the 356 cases and 19 deaths reported on April 22, 2020 [5]. Therefore, intensive research and innovation are required to provide new knowledge that can be utilized to improve supportive therapy; discover and develop new drugs, vaccines, and diagnostics; and initiate clinical trials in developed and developing countries around the world [3,5].

Although the need for ventilators and extracorporeal membrane oxygen for severe and critical cases of COVID-19 has been clarified [1,2,4], the immunopathogenesis of COVID-19 remains unclear [6]. However, emerging data from patients infected with COVID-19 indicate that genetic immunologic, metabolic, and environmental factors are involved in the pathogenesis of COVID-19 [6,7]. In addition to having no definitive treatment for COVID-19, there are also some supportive antiviral and

corticosteroid treatments whose use remain controversial [8,9], suggesting that evidence-based supportive treatments are needed to combat COVID-19 globally. Clinically, patients with SAR-CoV-2 infection tend to experience mild symptoms such as fever, dry cough, anosmia, fatigue, dyspnea, headache, diarrhea, and sore throat, with up to 20% of these patients developing vascular and systemic complications such as leukocyte infiltration of the lungs, pneumonia, severe pneumonia, acute respiratory distress syndrome (ARDS), sepsis, and septic shock [2,10]. Recent studies in patients with COVID-19 have also shown lymphopenia to be a common immunosuppressive factor associated with a critical course of disease characterized by severe vascular abnormalities and poor outcomes [11-13]. Lymphopenia refers to lymphocyte count <1000-1500 cells per microliter of blood [14,15]. Currently, there is limited knowledge on how patients with COVID-19 develop lymphopenia, which incidentally can occur at an early stage of the disease [16].

Association Between Lymphopenia, Leukocyte Apoptosis, Hypovitaminosis D, and Vasculitis

The fact that the biology of SARS-CoV-2 is closely related to SARS-CoV (severe acute respiratory syndrome–associated coronavirus), much can be learned from previous studies on patients infected with SARS. In the studies conducted by O'Donnell et al [17], Dancer et al [18], and Ding et al [19], lymphopenia was found to be associated with leukocyte apoptosis, low vitamin D status, and vascular dysfunction in Asian patients with SARS who exhibited different clinical manifestations. In Africa, leukocyte apoptosis has also been shown to play a role in the pathogenesis of several infectious diseases such as HIV, tuberculosis, and chronic obstructive pulmonary disease [20-22]. The FasL (Fas ligand)/Fas pathway, having caspase 3 as the key driver, represents the major leukocyte apoptosis pathway [23]. In addition, supporting

leukocyte apoptosis is the upregulation in gene expression of agonists such as the *Bax* gene and downregulation of antagonists like the *Bcl-2* and *BCL2L12* genes [24]. Apart from regulating bone mineral homeostasis, vitamin D as the active metabolite 1,25-dihydroxyvitamin D₃—abbreviated 1,25(OH)₂D₃—is an important immune modulator in humans in disease and health [25]. Studies have further revealed vitamin D to downregulate the expression of the acute phase and TH1 inflammatory cytokines such as IFN- γ , IL-1, IL-6, and TNF β in patients with respiratory diseases [26], indicating its immunosuppressive function. This also suggests that vitamin D may be beneficial in alleviating cytokine storm induced by lymphopenia and viremia in patients with COVID-19. Meanwhile, vitamin D deficiency has been shown to contribute to severe inflammatory response syndrome, sepsis, septic shock, and death [27,28], which are notable severe disease activities in patients with COVID-19. This finding also suggests that vitamin D supplementation in patients with COVID-19 may be beneficial clinically. This was actually evident in clinical trials reported by Batacchi et al [29] and Fanco et al [30] on the benefits of vitamin D supplementation in patients with chronic kidney and rheumatic diseases. The soluble vascular cell adhesion molecule-1 (svCAM-1) is a critical marker of vasculitis disorders such as diabetes, hypertension, cancer, systemic erythematosis, and rheumatoid arthritis. However, as a vasculitis disorder, the role of VCAM-1 in the pathogenesis of COVID-19 remains unknown [31,32].

Vitamin D Receptor Gene Polymorphism and Serum Vitamin D Level

Genetic evidence has further implicated polymorphisms—Apa1 (rs7975232), Fok1 (rs2228570), and Bms1 (rs1544410)—in the vitamin D receptor (VDR) gene to be responsible for hypovitaminosis D, suggesting that host genetic factors may be the cause of hypovitaminosis D in humans, as previously reported by Santos et al [33]. Hypovitaminosis D in humans has been shown to occur despite adequate exposure to sunlight [34]. The VDR is a member of the nuclear receptor family whose gene is located on chromosome 9 with 9 exons in the human genome. Its three functional polymorphisms have been mapped to exon 2 of the second methionine start site, intron 8, and the three prime untranslated region of the gene [35–37]. The functional effects of these polymorphisms include changes in VDR protein folding and size, alterations in mRNA processing, splicing, and editing, as well as the binding affinity to the DNA response element of the adjacent gene under regulation [35–37].

Rationale and Justification

To the best of our knowledge, there is a paucity of information on the burden of lymphopenia and its contribution to disease severity in African patients with COVID-19. No research efforts have been undertaken to investigate the pathophysiological relevance of hypovitaminosis D in the immunopathogenesis of lymphopenia coupled with the modulatory effects of VDR gene polymorphisms on the systemic level of vitamin D among SAR-CoV-2-negative, hospitalized patients with COVID-19 and survivors (ie, treated and recovered patients). Currently, like many African countries, vitamin D supplementation is not included in the treatment guidelines for hospitalized patients

with COVID-19 in Nigeria, and the clinical benefits of vitamin D supplementation as a supportive treatment remain unknown. There is also limited understanding of the interactions between possible phenotypic and genotypic determinants of lymphopenia among Africans without SARS-CoV-2 infection or hospitalized due to COVID-19 and those who have recovered from the disease after successful treatment. Apart from the established contribution of comorbid factors such as diabetes, hypertension, hepatitis B and C, and HIV to the progression of SARS-CoV-2 infection with severe outcomes, the poor management of infected patients with repurposed drugs also contributes to poor prognosis. Therefore, an understanding of the interplay of the genetic and phenotypic determinants of the pathophysiological drivers of COVID-19 severity in African patients is needed. This study will aid in the stratification of COVID-19-infected Nigerian patients with and without lymphopenia phenotypically and genotypically to enable biomarker discovery and pave the way for the appropriate and timely deployment of patient-centered treatments with repurposed drugs to improve prognosis.

This pilot study aims to investigate the role of low vitamin D status, vasculopathy, apoptotic pathways, and VDR gene polymorphisms in the immunopathogenesis of lymphopenia among Nigerian patients infected with SARS-CoV-2.

Specific Objectives

The study objectives are as follows:

1. Determine the prevalence and distribution of lymphopenia among Nigerian patients with COVID-19 at two selected health facilities in Lagos, Nigeria;
2. Examine serum vitamin D, FasL, and VCAM-1 levels in relation to the stages of COVID-19 infection among these patients compared to SARS-CoV-2-negative controls;
3. Evaluate the correlation of VDR gene polymorphism with serum vitamin D level and disease activity (mild symptoms, pneumonia, ARDS, and sepsis) of patients with COVID-19 who do or do not exhibit comorbidities;
4. Assess the level of expression of apoptotic agonist (*Bax*) and antagonists (*Bcl-2*, *BCL2L12*) in participants with and without SARS-CoV-2 infection;
5. Evaluate the relationship between lymphopenia and serum vitamin D, FasL, VCAM-1, and apoptotic markers in hospitalized patients with COVID-19.

Hypotheses

Our hypotheses are as follows:

1. Lymphopenia is associated with an increased susceptibility to SARS-CoV-2 infection and COVID-19 severity with and without comorbidities;
2. Lymphopenia is associated with a low level of vitamin D, which is worsened by the VDR—Apa1 (rs7975232), Fok1 (rs2228570), and Bms1 (rs1544410)—gene polymorphisms in hospitalized patients with COVID-19;
3. Higher upregulation of the *Bax* gene and downregulation of the *Bcl-2* and *BCL2L12* genes occur in hospitalized patients with COVID-19 compared to recovered patients and controls (ie, no SAR-CoV-2 infection);

- There is an inverse correlation of serum vitamin D with sVCAM-1, caspase 3, and soluble FasL (sFasL) levels in patients with SARS-CoV-2 infection, which does not exist in the controls.

Methods

Study Design

This quantitative study is cross-sectional in design. The participants will be recruited from the Nigerian Institute of Medical Research (NIMR) and the Infectious Disease Hospital (IDH) in Lagos. This study will be carried out over a period of 12 months (March 2020 to February 2021). It will involve questionnaire administration, hematological assays, flow cytometry, immunoassays, and molecular tests. The purpose of administering the questionnaire is to generate new data not reflected in the national epidemiological form for COVID-19 (such as history of/current treatment for tuberculosis; chronic obstructive pulmonary disease, and hospitalization in the previous 3 months prior to the onset of SARS-CoV-2-related symptoms) to improve the interpretation of test results and patients' disease diagnosis (see [Multimedia Appendix 1](#) for questionnaire).

SARS-CoV-2 diagnosis in patients will be based on a one-step real-time reverse transcription-polymerase chain reaction (rRT-PCR) test using nasopharyngeal swab samples at both study sites. Each swab sample will be collected in 3 mL of sterile viral transport medium (Rocky Mountain Biologicals, LLC). The rRT-PCR test per sample will be done by two independent, trained analysts whose results will be blinded from each other. Suspected patients whose rRT-PCR test reveals a negative result for 3 successive days using fresh nasopharyngeal samples and without progression of symptoms at presentation (to rule out false negative results) will be categorized as "SARS-CoV-2 negative." Those who are SARS-CoV-2 positive but present mild symptoms will be called "COVID-19 mild." Both categories of patients will be recruited at NIMR. The other two categories of patients—SARS-CoV-2-positive patients hospitalized due to complications (such as severe pneumonia, pulmonary edema, ARDS, pulmonary thrombosis, sepsis, and septic shock) and previously hospitalized COVID-19-confirmed (ie, rRT-PCR positive) patients who recovered from the disease—will be recruited at IDH. Some patients with COVID-19 who present mild or moderate symptoms will also be recruited as participants at IDH. Participant enrollment will be carried out consecutively until the desired sample size is acquired.

Study Sites

The study will be conducted at NIMR and IDH. Established in 1977, NIMR is the leading national research institution in Nigeria, with the mandate to conduct basic, applied, translational, implementation, and clinical research on diseases of public health importance in the country. The NIMR Center for Human Virology and Genomics is one of the national SARS-CoV-2 diagnostics laboratories in the country handling preparedness and response to the COVID-19 pandemic in Nigeria. The center has rRT-PCR and Sanger sequencing facilities to detect and confirm SARS-CoV-2 diagnoses from

nasopharyngeal and oropharyngeal swab samples. IDH is a specialist hospital involved in the diagnosis and treatment of patients with infectious diseases such as multidrug-resistant tuberculosis, HIV, and Lassa fever. Patients infected during the 2014 Ebola outbreak in Nigeria were also managed in this hospital. The hospital has a biosafety level 3 laboratory for emerging and re-emerging human and zoonotic pathogen containment in the country. In response to the current COVID-19 pandemic in Nigeria, IDH has also been given the responsibility of SARS-CoV-2 detection by rRT-PCR. In addition, the hospital has isolation and treatment centers with a good triage system to manage infected patients with mild, moderate, and severe manifestations of COVID-19. The hospital also has an intensive care unit with expert frontline health personnel such as cardiologists, pulmonary medicine physicians, and intensivists for the management of severe COVID-19 cases.

Sample Size Determination and Study Population Grouping

The minimum sample size for the present study has been calculated based on the assumptions outlined below and using the following formula [38]:



where n is the sample size, z represents the study confidence level for a two-tailed test at 1.96, p is the average prevalence rate of COVID-19 globally at 5.8% [1,2], and d is an error rate of 5%. By substituting the assumptions above into the formula, we obtained: $n = (1.96^2 \times 0.058 \times [1-0.058]) \div 0.05^2 = 83.9$. This was approximated to 84. This was followed by the addition of 10% to the calculated sample size to account for nonresponse and a design effect of 2.5 to provide a total sample size of 230 participants. The number of participants to be enrolled into the four groups of suspected and confirmed cases of COVID-19 was determined as follows:

- Group 1: participants who are SARS-CoV-2 negative at NIMR comprise 30% of the total sample size of 230 ($n=69$);
- Group 2: participants with SARS-CoV-2 infection who present mild or moderate symptoms of COVID-19 and are hospitalized at NIMR and IDH for isolation and treatment comprise 14% of 230 ($n=32$);
- Group 3: SARS-CoV-2 infected participants with severe manifestations of COVID-19 who are hospitalized at IDH comprise 40% of 230 ($n=92$);
- Group 4: previously hospitalized COVID-19-confirmed patients (rRT-PCR positive) who were treated at IDH and have recovered comprise 16% of 230 ($n=37$).

The percentage of the total sample size apportioned for each group of the participants was based on authors' assumptions but also guided by the pattern of cases seen at the study sites (unpublished).

Inclusion and Exclusion Criteria

For group 1 participants, the inclusion criteria are as follows: aged ≥ 15 years with or without selected comorbidities, and suspected of SARS-CoV-2 infection but tested negative by rRT-PCR.

For group 2 participants, the inclusion criteria are as follows: aged ≥ 15 years with or without selected comorbidities, with laboratory results indicative of SARS-CoV-2 infection by rRT-PCR and exhibition of mild or moderate symptoms, and admitted to the isolation center at IDH.

For group 3 participants, the inclusion criteria are as follows: aged ≥ 15 years with or without selected comorbidities, with laboratory results indicative of SARS-CoV-2 infection by rRT-PCR, and hospitalized in the treatment center for the management of the exhibited COVID-19 complications.

For group 4 participants, the inclusion criteria are as follows: aged ≥ 15 years with or without selected comorbidities, and previously hospitalized but recovered after treatment.

For all four groups, the exclusion criteria are as follows: incomplete metadata from the questionnaire and case report form, a diagnosis of cancer or end-stage renal disease, and declined consent by the individual to participate in the study.

The case definitions for these groups and definitions of selected comorbidities are provided in [Textbox 1](#).

Textbox 1. Variables and definitions.

<p>Participant groups:</p> <ul style="list-style-type: none"> • SARS-CoV-2–negative patients: 3 successive negative test results by real-time reverse transcription–polymerase chain reaction (rRT-PCR) using a fresh nasopharyngeal swab sample per test and without progression of clinical symptoms elicited at presentation at the Nigerian Institute of Medical Research (NIMR) • SARS-CoV-2–positive patients with mild or moderate symptoms of COVID-19: positive test results by rRT-PCR using a nasopharyngeal swab sample with at least two of the following symptoms: fever (axillary temperature >37.4 °C), dry cough, sore throat, anosmia, fatigue, myalgia, headache, vomiting, diarrhea, and pneumonia • SARS-CoV-2–positive patients with COVID-19 complications: hospitalized patients with positive test results via rRT-PCR using nasopharyngeal swab sampling with at least two of the following complications: severe pneumonia, pulmonary edema, sepsis, septic shock, pulmonary thrombosis, and organ failure, as provided in the case report form by the attending physician coupled with the need for ventilation (mechanical or automated) or extracorporeal membrane oxygenation • Recovered patients: previously hospitalized patients with confirmed COVID-19 (ie, rRT-PCR positive), with or without the selected comorbid factors, who have been discharged following successful treatment, as confirmed by 2 negative SARS-CoV-2 rRT-PCR test results 24 hours apart <p>Selected comorbidities:</p> <ul style="list-style-type: none"> • Hypertension: systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or both, and on antihypertensive medication irrespective of blood pressure status • Diabetes mellitus: fasting blood sugar ≥ 126 mg/dL or on medications for diabetes • Tuberculosis: <i>Mycobacterium tuberculosis</i> culture positive, GeneExpert <i>M. tuberculosis</i> positive with or without rifampicin resistance using sputum sample or on medication for <i>M. tuberculosis</i> infection per national treatment guidelines • Chronic obstructive pulmonary disease: exhibiting symptoms of a chronic cough, sputum production, difficult or labored breathing, and a spirometry FEV1 between 50%-79% of the predicted normal values and an FEV1/FVC ratio $<70\%$ • Pneumonia: pulmonary disease with symptoms of fever, cough, chest pain, and rapid breathing >20 beats per minute at rest or shortness of breath • Severe pneumonia: pneumonia characterized by hypoxemic respiratory failure, ventilation support, and sepsis • HIV: HIV-1 seropositive or on medication for HIV/AIDS • Hepatitis: on medications for hepatitis B or C • Lymphopenia: total blood lymphocytes <1000-1500 cells per microliter of blood • Vitamin D deficiency: values of 25(OH) D of ≤ 50 nmol/L (20 ng/mL) • Vitamin D insufficiency: values of 25(OH) D ranging from 52 to 72 nmol/L (21-29 ng/mL) • Hypovitaminosis D: values of 25(OH) D <75 nmol/L (30 ng/mL) • Normal vitamin D status: values of 25(OH) D of ≥ 75 nmol/L (30 ng/mL) were considered sufficient for vitamin D
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Ethical Approval and Consent to Participate

This study has been submitted for approval to the NIMR Ethics Committee; approval for patient recruitment and access to sample collection at IDH has already been granted. Participants are required to give consent of participation in the study prior to enrollment. All data obtained from each study participant will be kept confidential and accessed only by the managing physician in charge for use in case management.

Data Collection

Sociodemographic data (eg, age, gender, marital status, occupation, education), clinical data (diabetes, hypertension, hepatitis, HIV, need for ventilator or extracorporeal membrane oxygen, COVID-19 status), and travel history data (domestic and international travel to and from Lagos within 14 days of illness onset) of the participants will be collected using a structured questionnaire prepared in English. Anthropometric measurements of weight to the nearest 0.1 kg and height to the

nearest 0.1 m will be performed using a meter rule and a digital weighing scale (Tanita Corp) with the patients bare footed and wearing light clothing. BMI will be computed with overweight and obesity classified as BMI ≥ 25 kg/m² and BMI ≥ 30 kg/m², respectively. The questionnaire will be pretested at the Lagos State University Teaching Hospital on 10 hospitalized patients to assess its comprehensibility and timeliness of administration with identified gaps corrected prior to data collection at the selected study sites. For severe and clinical cases, the attending clinician will assist and supervise data collection via a review of the case report form of the affected participants. Each participant's questionnaire will be confirmed for completeness, and data coding will be done by the principal investigator prior to data entry into spreadsheets. Generally, the metadata collected from the participants will be blinded from analysts involved in SARS-CoV-2 infection confirmation by rRT-PCR.

Laboratory Methods

Sample Collection and Processing

From every COVID-19-confirmed or treated case, an aliquot of 3 mL of venous blood obtained by venipuncture will be collected into an EDTA (ethylenediaminetetraacetic acid) vacutainer tube with 2 mL processed to obtain the buffy coat for molecular assays. Another aliquot of 3 mL venous blood will be collected in a plain bottle, allowed to clot, centrifuged at 2000 rpm for 10 minutes, and have its serum collected into a new bottle for serological and biochemical assays. Both sample types will be labeled using each study participant's unique ID along with the date of collection, sample type, and study site. The processed samples will be stored at -80 °C prior to laboratory assays.

Blood Lymphocyte Count

A 0.5 mL aliquot of blood sample collected into the EDTA vacutainer tube will be used for white blood cells measurement. This will be done on fresh samples using the ADVIA 120 Hematology System. In the absence of a national surveillance range of lymphocyte counts in the Nigerian general population, a lymphocyte count less than 1000/ μ L will be considered as lymphopenia, as used by previous investigators in Nigeria and other parts of the world [14,15].

Measurement of Plasma sVCAM-1 and sFasL

The levels of sVCAM-1 and caspase 3 will be measured by an enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Inc). sFasL levels were also measured by the ELISA kit (Bender Medsystems) in serum. The interassay variation coefficients of the two assay kits range from 2.5%-4.5%. Serum aliquot at 0.1 mL will be used for each individual ELISA as previously described [39,40].

Measurement of Serum 25(OH) D Concentrations

The serum 25(OH) D level will be measured by a competitive ELISA (kit provided by DRG International, Inc). Values of 25(OH) D ≤ 50 nmol/L (20 ng/mL) will be used to indicate vitamin D deficiency; values ranging from 52 to 72 nmol/L (21-29 ng/mL) will be considered as vitamin D insufficiency, and levels of ≥ 75 nmol/L (30 ng/mL) will be considered as sufficient levels of vitamin D [41].

DNA Extraction

Genomic DNA will be extracted from the buffy coat using the QIAamp DNA extraction kit (Qiagen) according to the manufacturer's protocol. The extracted DNA will be suspended in TE buffer (pH 8.0) and stored at 4 °C prior to use. Isolated DNA concentration will be estimated using a nanodrop spectrophotometer at 260 nm and measured in ng/ μ L. Purity will be assessed based on an absorbance ratio of 260 nm to 280 nm ($A_{260\text{nm}}/A_{280\text{nm}}$) with values ranging from 1.65-2.0 regarded as good quality.

RNA Extraction

One milliliter of EDTA blood will be used for total RNA extraction with the QIAamp RNA blood mini kit, following the procedure provided by the manufacturer (Qiagen). The spin column-bound RNA will be eluted with 50 mL of RNase-free water. To detect SARS-CoV-2, RNA will also be isolated from the 200 μ L of nasopharyngeal swab samples using the Qiagen RNeasy mini extraction kit, following the manufacturer's instructions (Qiagen). The spin column-bound RNA will be isolated with 50 mL of the provided elution buffer. Both RNA samples per participant will be stored at -80 °C. RNA yield will be estimated using a nanodrop spectrophotometer at 260 nm and measured in ng/ μ L. The isolated RNA solution with an $A_{260\text{nm}}/A_{280\text{nm}}$ value of 1.9-2.1 will be considered pure.

Gene Detection Assays

Both the apoptosis-related (*Bax*, *Bcl-2*, and *BCL2L12*) and VDR genes will be detected separately by monoplex polymerase chain reaction (PCR) with their specific primers, as shown in Table S1 in [Multimedia Appendix 1](#), using the isolated genomic DNA as a template [42-44]. For each sample, the 20 μ L reaction mixture will consist of a 5-fold dilution of the PCR master mix to give 1.5 mM MgCl₂, 200 μ M deoxynucleoside triphosphates (dNTPs), 1.25 U of Taq DNA polymerase and 1 \times PCR buffer, pH 8.8, as a final composition (Isodyne), 10 picomoles of each forward and reverse primers, and 2 μ L of genomic DNA template (approximately 100 ng). The final volume of the mixture will be adjusted to 20 μ L by adding nuclease-free water. The PCR reaction will be performed on the SimpliAmpli Thermal Cycler (Thermo Fisher Scientific). The amplification condition for each reaction has also been provided in Table S1 in [Multimedia Appendix 1](#). The PCR products derived from this procedure will be subjected to horizontal gel electrophoresis in 2% agarose gel prestained with ethidium bromide and a 100 bp DNA ladder marker for sizing. Both the visualization of the PCR bands and the sizing will be done under UV light using a photodocumentation gel dock (Thermo Fisher Scientific). Each PCR product will be diluted 10-fold and used as a template for real-time PCR.

RT-PCR

The production of first-strand complementary DNA (cDNA) from the RNA samples isolated from blood will be performed by the reverse transcription technique using oligo-dT primers. The 20 μ L RT-PCR reaction will consist of Super Script II Reverse Transcriptase (Thermo Fisher Scientific, Invitrogen) and will be carried out according to the manufacturer's protocol. The reaction will be performed on a heater block at 50 °C for

20 minutes. This will be followed by a 10-minute step at 99 °C to denature the enzyme, followed by cooling to 4 °C. The cDNA product will be stored at 4 °C and used for quantitative PCR (qPCR) within 24 hours of preparation.

Quantitative Real-Time PCR

The quantitative mRNA expression analysis of the apoptosis-related genes *Bax*, *Bcl-2*, and *BCL2L12* will be carried out using the real-time PCR method with SYBR Green 1 fluorescent dye [23,45]. The pair of primers designed for each of the genes under study can be seen in Table S1 in [Multimedia Appendix 1](#). The primers for the apoptosis-related genes have been designed from the published reference sequence of each gene in the National Center for Biotechnology Information (NCBI) database using the Primer3Plus (eg, GenBank accession numbers NM_000633.2, NM_138761.3, NM_138639.1 and NM_002046.4 for *BCL-2*, *BAX*, *BCL-x*, and *GAPDH*, respectively). The *GAPDH* gene for glyceraldehyde 3-phosphate dehydrogenase was used as the internal control for all qPCR reactions. The qPCR reaction for each sample will be performed on an ABI Prism 7500 Thermal Cycler (Applied Biosystems) in duplicates, so as to address any data reproducibility issues. The 10 µL reaction mixture will consist of 0.5 µL of cDNA (for *BAX*, *BCL2L12*, and *GAPDH*) or a 10-fold diluted VDR PCR product, 50 picomoles of gene-specific primers, and 5 µL of Power SYBR Green I PCR master mix (Applied Biosystems, 4367659), containing AmpliTaq Gold DNA polymerase. The thermal conditions will consist of an initial denaturation and activation of a hot-start DNA polymerase step at 95 °C for 10 minutes, followed by 40 cycles of denaturation at 95 °C for 15 seconds and primer annealing and extension at 60 °C for 1 minute. After the quantitative amplification, a dissociation curve analysis will be performed to distinguish the amplified sequences of interest from any nonspecific ones or primer dimers via comparison of the melting temperatures of the formed PCR amplicons. The relative quantity of the mRNAs will be normalized relative to that of *GAPDH*, while the relative fold changes in the transcription level of these genes between asymptomatic and clinical cases, recovered and clinical cases, and asymptomatic and recovered cases will be calculated based on their cycle threshold (Ct) values using the comparative Ct method ($2^{-\Delta\Delta C_t}$) [46]. qPCR amplification efficiency will be ascertained by performing a validation experiment as described by Kontanis et al [47] where amplification efficiency equals $10^{-1/\text{slope}}$.

One-Step rRT-PCR

For the diagnosis of SARS-CoV-2 infection, rRT-PCR will be carried out with RNA samples isolated from nasopharyngeal swabs as a template using the Viasure one-step rRT-PCR SARS-CoV-2 detection kit (CerTest Biotec). Briefly, 5 mL of isolated nasopharyngeal RNA, reconstituted SARS-CoV-2-positive control (noninfectious synthetic SARS-CoV-2 cDNA), or negative control will be added to each of the well strips containing specific primers and probes (targeting SARS-CoV-2 Orf1ab, N gene, and an internal control [IC]), buffer, dNTPs in a stabilized format prehydrated with 15 mL of supplied rehydration buffer. After a brief centrifugation, the one-step rRT-PCR will be done in a Bio-RadCFX96

Real-Time PCR Detection System (Bio-Rad) programmed as follows: 1 cycle of reverse transcription at 45 °C for 15 minutes, 1 cycle of initial denaturation at 95 °C for 2 minutes, followed by 45 cycles of denaturation at 95 °C for 10 seconds and an annealing/extension step at 60 °C for 50 seconds. Both positive and negative controls are included in each run to validate the reaction based on the absence of signals in the negative control well. Fluorogenic signals will be collected in the FAM (Orf1ab gene), ROX (N gene) and HEX (IC) channels of the CFX96 detection system. The signal generated by IC will be used to verify amplification. An rRT-PCR test for a sample will be regarded as positive if an amplification curve is generated for Orf1ab gene, N gene, and positive control with a Ct value less than 38 with or without an IC amplification curve. A presumptive test is indicated by the absence of the Orf1ab signal but presence of an amplification curve for the N gene and positive control with or without the IC amplification curve. A SARS-CoV-2 negative test will be indicated by the absence of an amplification curve for the Orf1ab gene and N gene but presence of amplification curves for the IC and positive control. All presumptive tests will be confirmed by repeating RNA isolation and pooling both RNA samples to increase RNA yield prior to rRT-PCR and combining epidemiological and clinical data for a SARS-CoV-2 diagnosis.

Genotyping of VDR Gene Polymorphisms

Genotyping for the Apa1 (rs7975232), Bsm1 (rs1544410), and Fok1 (rs2228570) polymorphisms in the VDR gene will be done using a PCR restriction fragment length polymorphism method as previously described [40–42]. Amplification was performed using a SimpliAmpli Thermal cycle (Thermo Fisher Scientific). The 20 µL reaction mixture will consist of a 5-fold dilution of PCR master mix to give 1.5 mM MgCl₂, 200 µM dNTPs, 1.25 U of Taq DNA polymerase and 1 × PCR buffer, pH 8.8, as final composition (Isodyne), 10 picomoles of each forward and reverse primers, and 2 µL of genomic DNA template (approximately 100 ng). The final volume of the mixture will be adjusted to 20 µL by adding nuclease-free water. All PCR products will be digested with restriction enzymes (Fermentas–Euromedex), and the fragments will be separated by electrophoresis in a 3% agarose gel prestained with ethidium bromide (Table S1 in [Multimedia Appendix 1](#)). The Apa1, Bsm1, and Fok1 genotypes were defined by capital letters [42–44].

Capillary Sequencing of the VDR Gene and qPCR Amplicon

For quality control, a one-tenth of each of the VDR and qPCR amplicons will be randomly selected and cleaned using the EXOZAP reagent (Thermo Fisher Scientific). The cleaned amplicons will be sequenced at the Central Research Laboratory, a NIMR core sequencing facility, using a BigDye Terminator, version 3.1 (Thermo Fisher Scientific, Applied Biosystems), and appropriate primers (Table S1 in [Multimedia Appendix 1](#)). Each sequencing PCR reaction will contain 4 µL of the purified PCR product, 1.5 µL primer at 3.2 µM, and 2 µL of BigDye Terminator (Applied Biosystem). The PCR product will be further cleaned with HT ExoSAP. Finally, the contents of each well will be transferred to MicroAMP plates and then inserted

in the Seqstudio for electrophoresis and data analysis (Thermo Fisher Scientific). The raw data obtained after electrophoresis will be stored as an *.abi file and then processed by base calling peaks of different colors representing adenine, cytosine, thymine, and guanine bases according to the fluorescence intensity of each of these peaks. For VDR gene, multiple sequence alignment will be done to confirm single nucleotide polymorphisms (SNPs) designed by Apa1, Bsm1, and Fok 1 in the PCR restriction fragment length polymorphism assays using the MEGA omega software. For the qPCR amplicons, the NCBI Basic Local Alignment Search Tool will be used to confirm the amplified SARS-CoV-2 N genes.

Statistical Analysis

Coded data will be double entered into Microsoft Excel and Microsoft Access 2013 spreadsheets (Microsoft Corp). Data will be checked to ascertain the correctness and validity of each entry from the questionnaire before transfer for analysis. The entered data will be password protected and each record per participant will be given a unique identifier. Statistical analysis will be performed using SPSS (version 22.0, IBM Corp).

Fold changes in the expression levels of apoptosis-related genes (*Bax*, *Bcl-2*, *BCL2L12*) will be illustrated with a bar graph. Categorical data such as lymphopenia, gender, age group, and prevalence of hypovitaminosis D will be summarized as counts and percentages and analyzed by the chi-square test. The Kolmogorov-Smirnov test will be performed to confirm the normality of variables. The assumed continuous and normally distributed variables such as VCAM-1, FasL, serum vitamin D, and caspase 3 levels will be summarized as mean and standard error of mean and analyzed using the Student *t* test (2 categories of participants) and one-way analysis of variance (ANOVA) (3 or 4 categories of participants). For variables whose data are not normally distributed, the median will be computed. For such variables, comparison between two groups will be performed using the Mann-Whitney *U* test, while the Kruskal-Wallis test will be performed to compare 3 or 4 categories of participants. Analyses will be further stratified by comorbid factors such as diabetes, hypertension, HIV, obesity, chronic obstructive pulmonary disease, asthma, and hepatitis to reduce bias. These tests will also be used to evaluate the association between VDR polymorphisms, serum vitamin D, sVCAM-1, and FasL levels. Logistic regressions with odd ratios and 95% CIs calculated via a recessive model will be used to test the association of each of the VDR SNPs with COVID-19 severity among hospitalized participants. Pearson correlation coefficient analysis will be used to test the correlation of lymphopenia with vitamin D, sVCAM-1, sFasL, and caspase 3 levels. The Hardy Weinberg equilibrium principle will be used to examine the distribution

of VDR alleles and genotypes for each of the studied SNPs. The haplotype frequency of the 3 VDR functional SNPs will also be compared across participant groups using the chi-square test and have their linkage disequilibrium determined. Outcome of analyses with $P < .05$ will be considered significant.

Results

A total of 45 participants comprising 37 SARS-CoV-2-negative and 8 COVID-19-recovered individuals have been enrolled so far; their complete blood counts and CD4 T lymphocyte counts have been determined, and their serum samples and genomic DNA and RNA samples have been extracted and stored at -20°C until further analyses. The study is still in the recruitment phase, which is expected to be completed in November 2020. However, immunological and molecular assays of RNA and DNA samples already isolated will be done in parallel.

Discussion

The prevalence of COVID-19 and its associated adverse outcomes and economic constraints in Nigeria continue to increase. Therefore, it is important to understand the role of lymphopenia in the clinical outcome of SARS-CoV-2 infection and its underlying mechanisms. There is evidence that leukocyte apoptosis could contribute to lymphopenia and, together with hypovitaminosis D and vasculopathy, result in severe manifestations of the previous human coronavirus pandemics caused by SARS and the Middle East respiratory syndrome. However, the contributions of these pathophysiological factors to SARS-CoV-2 infection susceptibility and COVID-19 severity, especially among people in Africa, remain unclear. This information is very important for guiding an understanding of the immunopathogenesis of lymphopenia based on the influence of environmental, metabolic, apoptotic, and genetic factors among Nigerians. This translational research approach will further help in stratifying Nigerians infected with SARS-CoV-2 for treatment with an appropriate and timely repurposed drug regimen to improve prognosis. Discovering the role of VDR polymorphism in the occurrence of vitamin D deficiency and insufficiency among patients with SARS-CoV-2 infection will provide insight into how the clinical benefits of vitamin D supplementation can be optimized for those infected and/or hospitalized due to COVID-19 to reduce mortality, accelerate recovery from the illness, and promote health among people in Nigeria. This study will also explore the potential deployment of VDR genotyping and apoptosis-related immunological and molecular assays as components of the laboratory work-up of SARS-CoV-2-infected Nigerians to further improve the quality of care of patients with COVID-19 in the country.

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Authors' Contributions

BAI conceptualized the study and was involved in study design. AO and OA were also responsible for study design. BAI and OA were involved in molecular assays, and BAI, OA, and AO were involved in immunological and metabolic assays as well as

results interpretation. BAI, OO, EA, and OSI were involved in data collection. OO and OSI performed data analysis. All authors were involved in the preparation and review of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Supplementary materials.

[[DOCX File, 24 KB - resprot_v10i3e21242_app1.docx](#)]

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Abbreviations

ANOVA: analysis of variance

ARDS: acute respiratory distress syndrome

cDNA: complementary DNA

Ct: cycle threshold

dNTP: deoxynucleoside triphosphate

EDTA: ethylenediaminetetraacetic acid

ELISA: enzyme-linked immunosorbent assay

FasL: Fas ligand

IC: internal control

IDH: Infectious Disease Hospital

NCBI: National Center for Biotechnology Information

NIMR: Nigerian Institute of Medical Research

PCR: polymerase chain reaction

qPCR: quantitative polymerase chain reaction

rRT-PCR: real-time reverse transcription–polymerase chain reaction

RT-PCR: reverse transcription–polymerase chain reaction

SARS: severe acute respiratory syndrome

SARS-CoV: severe acute respiratory syndrome–associated coronavirus

sFasL: soluble Fas ligand

SNP: single nucleotide polymorphism

sVCAM-1: soluble vascular cell adhesion molecule-1

VCAM-1: vascular cell adhesion molecule-1

VDR: vitamin D receptor

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Protocol

Molecular and Cellular Biomarkers of COVID-19 Prognosis: Protocol for the Prospective Cohort TARGET Study

Patricia Kurizky^{1,2*}, MD, PhD; Otávio T Nóbrega^{1*}, PhD; Alexandre Anderson De Sousa Munhoz Soares^{1*}, MD, PhD; Rodrigo Barbosa Aires^{1*}, MD; Cleandro Pires De Albuquerque^{1,2*}, MSc, MD; André Moraes Nicola^{1*}, MD, PhD; Patrícia Albuquerque^{3*}, PhD; Andréa Teixeira-Carvalho^{4*}, PhD; Luciana Ansaneli Naves^{1,2*}, MD, PhD; Wagner Fontes^{5*}, MD, PhD; Isabelle Souza Luz⁵, BS; Liza Felicori^{6*}, PhD; Ana Paulo Monteiro Gomides^{7*}, MD, PhD; Dayde Lane Mendonça-Silva^{2,8*}, PhD; Laila Salmen Espindola^{1,8*}, PhD; Olindo Assis Martins-Filho^{4*}, PhD; Sheila Maria Barbosa de Lima^{9*}, PhD; Licia Maria Henrique Mota^{1,2*}, MD, PhD; Ciro Martins Gomes^{1,2*}, MD, PhD

¹Programa de Pós-graduação em Ciências Médicas da Faculdade de Medicina, University of Brasília, Brasília, Brazil

²Hospital Universitário de Brasília, University of Brasília, Brasília, Brazil

³Faculdade de Ceilândia, University of Brasília, Brasília, Brazil

⁴Fundação Oswaldo Cruz, FIOCRUZ-Minas, Belo Horizonte, Brazil

⁵Instituto de Ciências Biológicas, University of Brasília, Brasília, Brazil

⁶Instituto de Ciências Biológicas, Federal University of Minas Gerais, Belo Horizonte, Brazil

⁷Centro Universitário de Brasília, Brasília, Brazil

⁸Faculdade de Ciências da Saúde, University of Brasília, Brasília, Brazil

⁹Instituto de Tecnologia em Imunobiológicos Bio-Manguinhos, FIOCRUZ, Rio de Janeiro, Brazil

* these authors contributed equally

Corresponding Author:

Patricia Kurizky, MD, PhD

Programa de Pós-graduação em Ciências Médicas da Faculdade de Medicina

University of Brasília

Laboratório de Dermatologicologia - Faculdade de Medicina da UnB

Campus Universitário Darcy Ribeiro

Brasília, 70910-900

Brazil

Phone: 55 61 98114 8432

Email: patyshu79@gmail.com

Abstract

Background: Since the beginning of the COVID-19 pandemic, the world's attention has been focused on better understanding the relation between the human host and the SARS-CoV-2 virus, as its action has led to hundreds of thousands of deaths.

Objective: In this context, we decided to study certain consequences of the abundant cytokine release over the innate and adaptive immune systems, inflammation, and hemostasis, comparing mild and severe forms of COVID-19.

Methods: To accomplish these aims, we will analyze demographic characteristics, biochemical tests, immune biomarkers, leukocyte phenotyping, immunoglobulin profile, hormonal release (cortisol and prolactin), gene expression, thromboelastometry, neutralizing antibodies, metabolic profile, and neutrophil function (reactive oxygen species production, neutrophil extracellular trap production, phagocytosis, migration, gene expression, and proteomics). A total of 200 reverse transcription polymerase chain reaction-confirmed patients will be enrolled and divided into two groups: mild/moderate or severe/critical forms of COVID-19. Blood samples will be collected at different times: at inclusion and after 9 and 18 days, with an additional 3-day sample for severe patients. We believe that this information will provide more knowledge for future studies that will provide more robust and useful clinical information that may allow for better decisions at the front lines of health care.

Results: The recruitment began in June 2020 and is still in progress. It is expected to continue until February 2021. Data analysis is scheduled to start after all data have been collected. The coagulation study branch is complete and is already in the analysis phase.

Conclusions: This study is original in terms of the different parameters analyzed in the same sample of patients with COVID-19. The project, which is currently in the data collection phase, was approved by the Brazilian Committee of Ethics in Human Research (CAAE 30846920.7.0000.0008).

Trial Registration: Brazilian Registry of Clinical Trials RBR-62zdkk; <https://ensaiosclinicos.gov.br/rg/RBR-62zdkk>

International Registered Report Identifier (IRRID): DERR1-10.2196/24211

(*JMIR Res Protoc* 2021;10(3):e24211) doi:[10.2196/24211](https://doi.org/10.2196/24211)

KEYWORDS

COVID-19; TARGET; cytokine profile; neutrophil function; thromboelastometry; neutralizing antibodies; metabolomics; proteomics; biomarker; prognosis; design; cohort; virus; immunology; immune system; genetics

Introduction

COVID-19 emerged in the city of Wuhan, Hubei, China and spread worldwide over the next several months [1]. Originally reported by the World Health Organization (WHO) as a pneumonia outbreak of undetermined origin, COVID-19 had its epidemiological status revised by the WHO as a Public Health Emergency of International Concern by the end of January 2020 and as a pandemic at the beginning of March 2020 [2]. The etiologic agent was identified as a new coronavirus of the *Betacoronavirus* genus, named SARS-CoV-2, due to its structural similarity to severe acute respiratory syndrome-related coronavirus (SARS-CoV), which also accounted for an outbreak in China in 2002-2003 [3]. The disease is characterized by fever, cough, and dyspnea, and can progress to pulmonary failure and lead to liver, heart, and kidney damage. Clinical management of severe cases requires respiratory assistance [4].

Angiotensin converting enzyme-2 (ACE2) mediates SARS-CoV-2 (and other coronaviruses) entry via clathrin-mediated endocytosis into type-2 pneumocytes and macrophages of the lung milieu [5,6]. ACE2 is a membrane-bound enzyme that converts active angiotensin II to inactive angiotensin (1-7). Thus, ACE2 blocks the unfavorable effects of angiotensin II action, including classic vasoconstriction in addition to inflammation and thrombosis. SARS-CoV-2 binding markedly impairs ACE2 catalytic activity by competitive inhibition, with increased in situ pulmonary inflammation and coagulation as detrimental outcomes of weakened counter regulation of the angiotensin II/AT1 receptor axis [7].

Hence, COVID-19 resembles a hyperimmune syndrome defined by potentially lethal hypercytokinemia due to overproduction of a set of proinflammatory mediators, including interleukins (IL-1 β , IL-2, IL7), granulocyte colony stimulating factor, interferon-gamma (IFN- γ), monocyte chemoattractant protein-1 (MCP-1), and tumor necrosis factor-alpha (TNF- α), which culminates in multi-organ failure [8,9]. In addition, the Th17-type response plays an important role in severe cases due to an additional proinflammatory overflow resulting from supraphysiological IL-1 β , IL-6, and TNF- α levels that contribute to edema formation [10]. The role of cortisol and prolactin in the modulation of the immune system has long been described [11,12], but their participation (if any) in the COVID-19-related “cytokine storm” remains unknown. Moreover, given the intimate interplay of inflammation with blood clotting, severe

patients usually show a hypercoagulable profile that leads to an increased frequency of pulmonary thromboembolism, deep vein thrombosis, and even heart and brain ischemia events [13,14].

In this context, it is also no surprise that the first treatment that reduced COVID-19 mortality, in a large randomized controlled trial (RECOVERY [Randomised Evaluation of COVID-19 Therapy]) [12,15], was dexamethasone, a corticosteroid [12]. However, it also showed that the effect seems to depend on the clinical stage of the disease, highlighting the need for further investigations into the course of the inflammatory response. Other anti-inflammatory treatments such as tocilizumab, an IL-6 receptor-blocking humanized antibody used to treat rheumatoid arthritis, were used (out of compassion) in patients with severe COVID-19 in China and Italy [16-18], with some clinical improvement. Similarly, another drug under evaluation is baricitinib, a JAK2 inhibitor approved for myeloproliferative neoplasms and rheumatoid arthritis that reduces Th17-type cytokine secretion by blocking AP2-associated protein kinase 1 [19]. However, the clinical efficacy of baricitinib against COVID-19 has yet to be proven. These studies support the assumption that a cytokine “storm” not only plays a role in COVID-19 pathophysiology but also has predictive prognostic value to monitor the evolution of mild and severe cases.

New metabolomics protocols can characterize metabolic pathways and provide a broad view of the impact of SARS-CoV-2 on the body. Both metabolome and proteome composition are dynamic and reflect genome expression under specific conditions [20-22]. Furthermore, these innovative combination protocols can help in understanding the metabolic profile of a given patient or group of patients [23] from urine, saliva, and blood samples [24]. The chemical profile substantially contributed to biological and medical research, leading to advancements in clinical medical practice [23].

This paper describes the design and rationale of a multicenter prospective cohort study aimed at evaluating the molecular and cellular immune signature of COVID-19 by assessing serum inflammatory mediators and regulatory chemokines of Brazilian patients with different clinical forms of the disease.

Methods

Study Design and Population

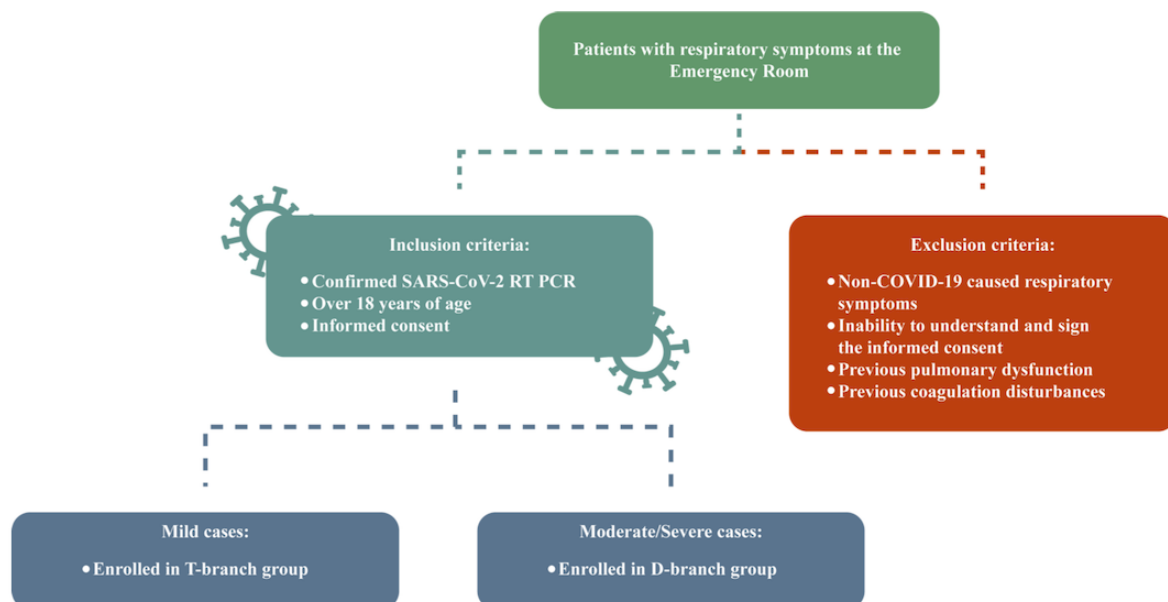
TARGET is registered in the Brazilian Clinical Trials database with registry code RBR-62zdkk and constitutes a multicenter, prospective cohort study of consecutive COVID-19 cases,

consisting of participants recruited from secondary and tertiary health care facilities in Brazil, namely, the University Hospital of Brasília (University of Brasília [UnB]) and the public regional hospitals of Asa Norte, Gama, Santa Maria, and Taguatinga (Brasília, Distrito Federal). Clinical procedures will be conducted according to a standard protocol approved by local institutional review boards under accession number CAAE 30846920.7.0000.0008, with participants included after voluntary signing of an informed consent form. The study protocol follows the recommendations of the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for observational studies [16].

Recruitment

Inclusion criteria will include the following: laboratory confirmation of COVID-19 by reverse transcription polymerase chain reaction (RT-PCR; KIT Molecular SARS-CoV2 [E/RP]; Bio-Manguinhos), a signed informed consent form, and older than 18 years. The exclusion criteria are as follows: patients with inconclusive, unavailable, or solely serological laboratory diagnosis of COVID-19; a dementia condition (Alzheimer, Parkinson, vascular frontotemporal, Lewy body, or others); schizophrenia or schizoaffective disorders with psychotic characteristics; and patients with previously known congenital hemorrhagic diseases or thrombophilia or use of anticoagulants (for coagulation tests; Figure 1).

Figure 1. Inclusion and exclusion criteria flowchart. The T-branch group is patients referred to the emergency room with mild or moderate forms of COVID-19 not requiring hospitalization. The D-branch group is patients referred to the emergency room with severe or critical forms of COVID-19 requiring hospitalization.



Clinical Assessment Protocol

The clinical evaluation aims to identify the signs and symptoms associated with COVID-19 and monitor the status (mild/moderate or severe/critical) of the disease. Clinical assessments include identification of comorbidities, COVID-19-associated symptoms and treatment, use of medications in general, clinical chemistry findings, and life support regimen care. Severe cases are defined for the purposes

of the study by dyspnea (respiratory rate >30 breaths per minute) coupled with any of the following criteria: pulsed wave oxygen saturation <93% at rest, $\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg, respiratory failure requiring mechanical ventilation, multiple organ failure, shock, or admission to the intensive care unit. Patients who do not meet the criteria for severe/critical forms will be considered mild/moderate cases. No asymptomatic patients will be included (Textbox 1 and Table 1).

Textbox 1. Components being assessed for characterization of the following domains: symptoms, comorbidities, treatments, biochemical profile, immune biomarkers, and leukocyte phenotype and functionality in the TARGET protocol.

Symptoms

Fever, chills, sneezing, sore throat, headache, cough, coryza, anosmia, dysgeusia, diarrhea, asthenia, nausea, vomit, dizziness, and others

Comorbidities

Pulmonary chronic disease, chronic cardiopathy, hypertension, diabetes, chronic kidney disease, pregnancy, neoplasms, smoking, alcohol ingestion, psoriasis, immunodepression, HIV, Dengue, hanseniasis, Zika virus, chikungunya, Chagas disease, yellow fever, leishmaniasis, malaria, H1N1, and others

Previous medications

Angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, nonsteroidal anti-inflammatory drugs, and others

Treatments aimed at COVID-19

Clinical support, dexamethasone, enoxaparin, chloroquine, antibiotics, ivermectin, nitazoxanide, lopinavir, ritonavir, remdesivir, immunoglobulin, plasmapheresis, anti-IL6, JAK inhibitor, and others

Biochemical tests

Leukocyte, lymphocyte and platelet counts, ferritin, lactate dehydrogenase, troponin, creatine kinase, aspartate aminotransferase, alanine aminotransferase, and creatinine

Hormone evaluation

Prolactin and cortisol

Thorax computed tomography

Ground-glass opacity (<25%, 25-50%, >50%)

Consolidation

Serum immune biomarkers

Chemokines: CXCL8, CCL11, CCL3, CCL4, CCL2, CCL5, and CXCL10; inflammatory cytokines: IL-1 β , IL-6, TNF- α , IL-12p70, IFN-gamma, IL-17A, and IL-15; regulatory cytokines: IL-1Ra, IL-4, IL-5, IL-9, IL-10, and IL-13; and cell growth factors: IL-2, IL-7, FGF-basic, PDGF, VEGF, G-CSF, and GM-CSF

Gene expression assays

IFN- γ , IL-12, IL-17a, TNF- α , IL-6, IL-4, IL-5, IL-10, IL-1b, RANTES, MCP-1, MIP, MIG, IP-10, and IL-8

Leukocyte phenotyping

CD3, CD4, CD8, HLA-DR, CD25, CD19, CD5, CD27, CD38, PD-1, CD28, CD14, CD16, and CD56

Leukocyte functionality

IL-1 β , IL-6, TNF- α , IFN- α , IL-5-PE, and IL-10

Metabolomic analysis

Metabolic profile/pathways

Neutrophils

Isolation, reactive oxygen species production, phagocytosis, neuroendocrine tumors production, migration assay, neutrophil proteomics

Table 1. The TARGET protocol will collect information about a series of characteristics and tests along the clinical evolution of patients with COVID-19. At each time point, the following data will be assessed.

Data registered	Day 0	Day 3	Day 9	Day 18
Age, gender, weight, and height	✓ ^a	— ^b	—	—
Symptoms	✓	✓	✓	✓
Contact with SARS-CoV-2 patient	✓	—	—	—
Reverse transcription polymerase chain reaction	✓	—	—	—
Time of symptoms	✓	—	—	—
Comorbidities	✓	—	—	—
Medications in use	✓	✓	✓	✓
SpO ₂	✓	✓	✓	✓
Thorax computed tomography	✓	✓	✓	✓
Biochemical tests	✓	✓	✓	✓
Supplementary oxygen	✓	✓	✓	✓
Mechanical ventilation	✓	✓	✓	✓
Death	✓	✓	✓	✓
COVID-19 treatment	✓	✓	✓	✓
Immune biomarkers	✓	✓	✓	—
Leukocyte phenotyping	✓	✓	✓	—
Cortisol/prolactin levels	✓	✓	✓	✓
Immunoglobulin profile	—	✓	—	—
D-dimer	—	—	✓	—
Thromboelastometry	—	—	✓	—
Neutralizing antibodies	—	—	—	✓
Metabolomic analysis	✓	✓	✓	✓
Gene expression	—	✓	✓	—
Neutrophils	—	—	✓	—

^aIndicates data was registered at this time point.

^bIndicates data was not registered at this time point.

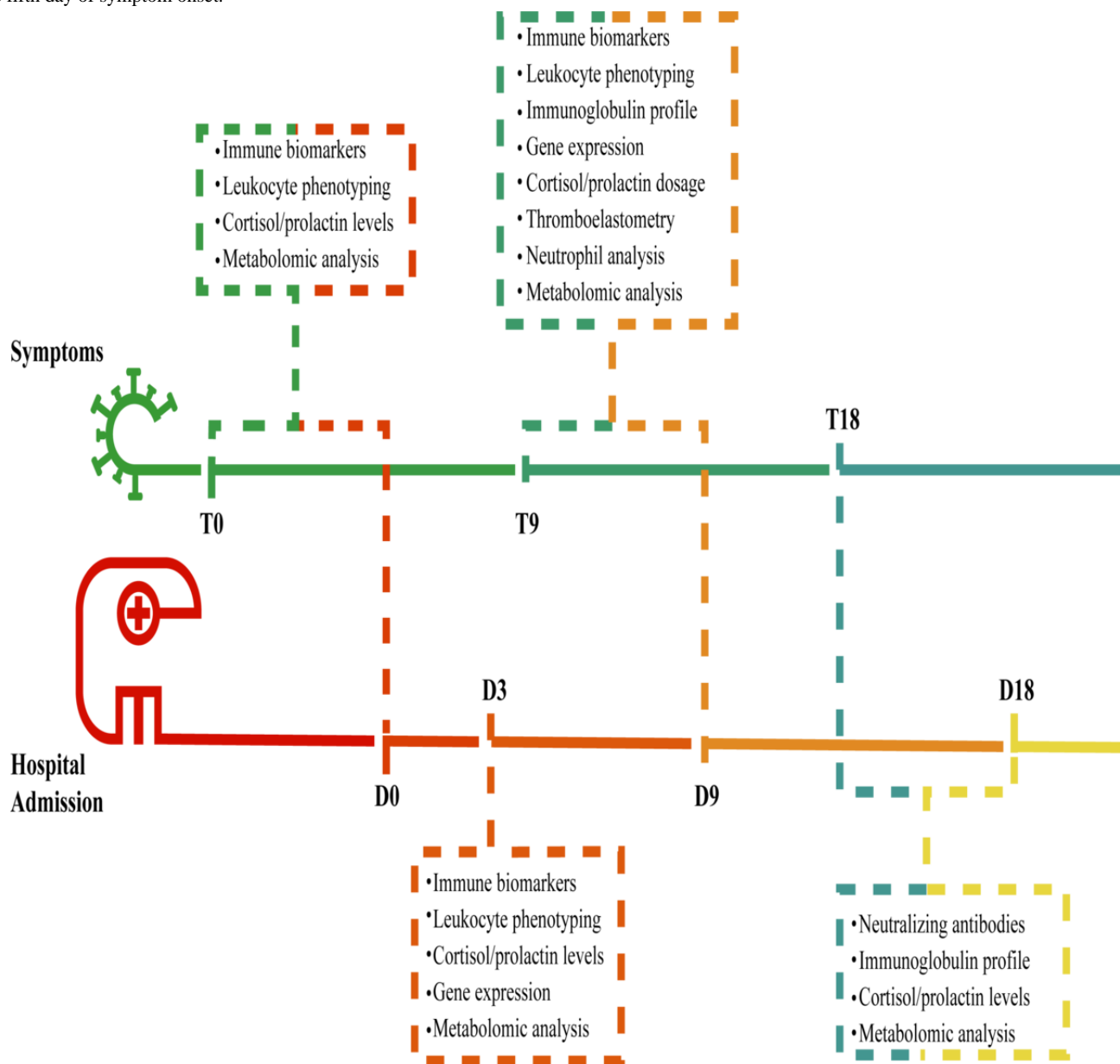
Timeline

The TARGET protocol comprises two arms, referred to as the timeline (T)-branch and the days of hospitalization (D)-branch. For the purposes of this study, the T-branch refers to patients with mild/moderate forms that did not require hospitalization. The D-branch refers to patients with severe/critical forms who required hospital admission. Patients on the T-branch will be analyzed on days 0, 9, and 18 (T₀, T₉, and T₁₈), while patients on the D-branch will be analyzed on days 0, 3, 9, and 18 (D₀, D₃, D₉, and D₁₈; [Figure 1](#)).

Biological Samples

The TARGET protocol encompasses the collection of blood samples in four different types of containers. For these purposes, whole peripheral blood samples will be collected in vacuum tubes without an anticoagulant (10 mL) to obtain serum samples for metabolomic and biochemical analysis, in sodium citrate (5 mL) for coagulation assays, and in heparin (10 mL) to obtain plasma samples and to isolate polymorphonuclear and peripheral blood mononuclear cells (PBMC). Samples will be collected at distinct time points as follows: day 0, at inclusion by confirmation of COVID-19; day 3, within 2-4 days after inclusion; day 9, within 7-10 days after inclusion; and day 18, within 15-20 days after inclusion ([Figure 2](#)).

Figure 2. Timeline showing the times of blood tests and the analysis performed. The upper line represents the duration of symptoms, a parameter used in the group of patients enrolled for prospective follow-up, composed primarily of patients who will evolve with mild conditions. The lower line represents the blood test dates in the hospitalized group: patients who have already entered the study with moderate to severe conditions, usually from the fifth day of symptom onset.



Preanalytical Sample Handling and Preprocessing

The whole blood samples will be processed to obtain serum or plasma samples and PBMC batches. Tubes will be centrifuged at 1900 g for 10 minutes at 22 °C to obtain serum or heparinized plasma and processed immediately within-facility for routine PBMC isolation and cryopreservation [17].

Clinical Biochemistry and Hematologic Analysis

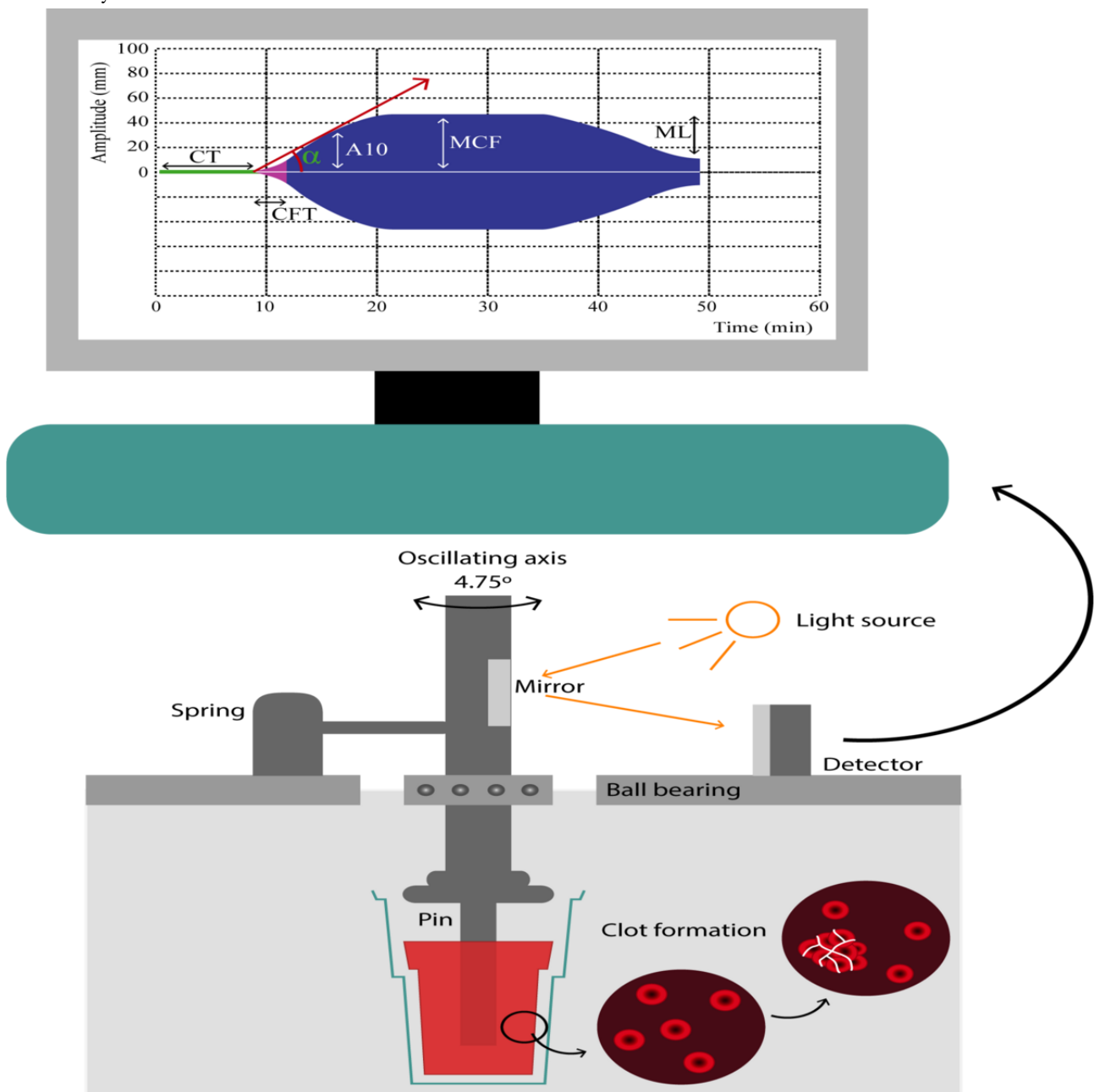
Plasma samples obtained in ethylenediamine tetraacetic acid will be immediately analyzed at local clinical laboratory facilities. Biochemical analysis will be performed with a Rocas Cobas E411 system using compatible reagents to assess the levels of ferritin, troponin T, creatine kinase, creatinine, aspartate aminotransferase, and alanine aminotransferase. All

procedures will be performed according to the manufacturer's recommendations. Cortisol and prolactin in serum samples will be quantified at the Sabin Medicina Diagnóstica (Brasília, Brazil) using the chemiluminescent method (Siemens, Advia Centaur). Hematological analyses will be performed using whole blood obtained in sodium citrate tubes in an ABBOTT Cell Dyn 3700 analyzer or equivalent with samples from days 0, 9, and 18.

The coagulation profile will be assessed at the DASA Laboratory (Brasília, Brazil) by thromboelastometry tests carried out within a 3-hour interval after blood collection [13,25] as follows: extrinsic system assay (EXTEM), intrinsic system assay (INTEM), fibrinogen assay (FIBTEM), and nonactivated

coagulation assay (NATEM; ROTEM, Werfen, Barcelona, Spain; Figure 3).

Figure 3. Thromboelastometry method for clot evaluation. A pin that spins around its own axis is put in contact with a citrated blood sample inside a cuvette. After recalcification and addition of a specific activator (depending upon the test), the clotting starts, and as it gets firmer, the spinning capacity of the axis is reduced, which is transformed by the system in a graphic representation of the clot, with increasing amplitude. As the fibrinolysis starts, the clot becomes less firm, which is represented as decreasing amplitude on the monitor. The extrinsic system assay (EXTEM)'s activator is thromboplastin and evaluates the extrinsic activation of coagulation. The intrinsic system assay's activator is elagic acid and evaluates the intrinsic activation of coagulation. The fibrinogen assay's activator is the same as EXTEM plus cytochalasin D, which inhibits platelet activity. This depicts only the participation of fibrinogen in the clot. The nonactivated coagulation assay is recalcified blood and is a nonactivated evaluation of coagulation. Circulating tissue factors, such as those expressed on monocytes in inflammatory states, will start the coagulation process. CT is the time frame from activation until an amplitude of 2 mm and represents thrombin formation. CFT represents the dynamic formation of thrombin and is the time frame between 2 mm and 20 mm of clot amplitude. A10 represents the clot amplitude 10 minutes after initiation and is directly related to MCF, enabling the clinic to make important decisions. MCF is the maximum amplitude of the clot and represents its main constituents, namely, fibrinogen and platelets. ML represents the percentage of clot reduction after initiation of fibrinolysis. Therefore, 60 minutes after initiation, thromboelastometry depicts important information about every phase of the coagulation process. A10: amplitude in 10 minutes; CFT: coagulation formation time; CT: coagulation time; MCF: maximum clot firmness; ML: maximum lysis.



Assessment of Molecular and Cellular Immunological Biomarkers

Serum biomarkers will be assessed using the Luminex Bio-Plex Pro platform set for 27 human immune mediators (Bio-Rad Laboratories, California) for the simultaneous assessment of the following analytes: chemokines (CXCL8, CCL11, CCL3, CCL4, CCL2, CCL5, and CXCL10), proinflammatory cytokines (IL-1 β , IL-6, TNF- α , IL-12p70, IFN- γ , IL-17A, and IL-15) and regulatory cytokines (IL-1Ra, IL-4, IL-5, IL-9, IL-10, and IL-13), and cell growth factors (IL-2, IL-7, FGF-basic, PDGF, VEG, G-CSF, and GM-CSF). All procedures will follow the manufacturer's recommendations, with levels obtained at days 0, 3, and 9.

The expression levels of immune mediators will be assessed by TaqMan quantitative RT-PCR (qRT-PCR) assays (Applied Biosystems, Foster City, CA) for each transcript, with retro-transcription set up with 1 ng/ μ L of RNA from PBMCs and from neutrophils. The reactions will be carried out on a QuantiStudio 3 Thermal Cycler (Applied Biosystems, CA) in standard mode [26]. Alternatively, qRT-PCR experiments for selected genes will be based on the SYBR Green (family of dyes for molecular biology) detection methodology using the SYBR Green PCR Master Mix and universal cycling conditions on the ABI Prism 7000 Sequence Detection System. Expression levels will be assessed on days 3 and 9.

Immunophenotypic/functional profiles of circulating leukocytes will be assessed upon short-term culture *in vitro*. The cell suspension will be stained with distinct panels of monoclonal antibodies comprising CD3, CD4, CD8, HLA-DR, CD25, CD19, CD5, CD27, CD38, PD-1, CD28, CD14, CD16, and CD56 for cell surface analysis, and IL-1 β , IL-6, TNF- α , IFN- α , IL-5-PE, and IL-10 for evaluation of intracytoplasmic functional status. Cells will be run on a FORTESSA flow cytometer (BD Bioscience, CA). An average of 100,000 cells will be analyzed per sample. The phenotypic/functional parameters will be assessed using FlowJo software (BD, New Jersey). Leukocyte phenotyping will be obtained at days 0, 3, and 9.

The immunoglobulin profile will be assessed by multiplexed PCR using cryopreserved PBMCs [19,27]. Sequencing libraries will be produced and sequenced using the Illumina MiSeq 2x300 bp platform. For each sample, 1 million reads corresponding to IgG and IgA will be produced. The reads will be processed using pRESTO [28], Ig heavy chain genes will be annotated using the MIXCR platform [29], and clonotypes will be determined as described in [30]. The immunoglobulin profile will be assessed in samples obtained on day 3.

Neutrophil Evaluation Experimental Design and Groups

Neutrophils will be obtained from healthy donors and from patients at two different times, T9/T18 and D9/D18. Neutrophils isolated from each donor will be divided into two aliquots and incubated in buffer (control group) or phorbol 12-myristate 13-acetate (PMA; activated group). Cells from each group will be submitted to the functional and molecular analyses described in the following sections.

Neutrophil Isolation and In Vitro Activation

Cell isolation will be performed from peripheral venous blood by centrifugation in Percoll gradients, as previously described [27]. The remaining erythrocytes will be removed by hypotonic lysis. Samples containing >95% neutrophils and >98% viable neutrophils will be prepared in 50% autologous plasma and divided into aliquots for control or activation in PMA [28].

Evaluation of Reactive Oxygen Species Production and Phagocytosis

The isolated neutrophils, after incubation in each condition, will be tested for reactive oxygen species production as described by Tahir et al [29].

Evaluation of Neutrophil Extracellular Traps Production

At the final 20 minutes of incubation in each condition, an aliquot of neutrophils will be removed and incubated with SYTOX green (high-affinity nucleic acid stain; 10 μ mol/L) and 4',6-diamidino-2-phenylindole (blue-fluorescent DNA stain; 1 μ g/mL). Fluorescence readings will be performed both by fluorescence microscopy and on a spectrophotometer [30].

Real-time Migration Assay

Neutrophils from each condition will be applied to the upper chamber of a xCELLigence Real-Time Cell Analysis instrument and dynamically measured regarding the migration toward the chemoattractant N-Formylmethionyl-leucyl-phenylalanine (potent polymorphonuclear leukocyte chemotactic factor) [31].

Neutrophil Proteomics

Neutrophils obtained in all experimental conditions will be subjected to cell lysis by ultrasound cavitation and then trypsin digested. Eluted peptides will be subjected to capillary chromatography in a two-column online vented system. The fractions will be eluted directly into the ionization chamber of an Orbitrap Elite mass spectrometer to be analyzed in data-dependent acquisition mode. The 20 most intense ions will be selected for high-energy collision dissociation fragmentation, and the fragments will be analyzed in the ion-trap detector. Mass spectra will be analyzed for protein quantification and identification using the Progenesis and Peaks software packages, as well as in-house developed R scripts for statistical analysis [32].

Metabolomic Profiling

We will aim to analyze each serum sample collected from mild (T-branch group) and severe (D-branch group) case patients and healthy volunteers at each time point in the same manner (Figures 1 and 2). Untargeted metabolomics will be performed using a Bruker UPLC-PDA-QqTOF (ultra-performance liquid chromatography photodiode array quadrupole-quadrupole-time-of-flight) compact (UPLC-MS/MS). The obtained data will be used to build molecular networking using the Global Natural Products Social Molecular Networking platform, which gives a better overview of the metabolic profile and group compound classes in clusters. For statistical validation of the metabolite differences between the groups, the data will be processed in MZmine and analyzed

by means of chemometric tools, as provided by the MetaboAnalyst platform. Based on this broad chemical outline, specific metabolites will be quantitatively analyzed using targeted metabolomics using a CLAE Quadrupole/Quadrupole. This approach will be used to validate and quantify specific components of interest, such as metabolites involved in the glycolytic and hexosamine pathways, and tricarboxylic acid cycle, among other possible biomarkers.

Sample Size Calculation

The sample size calculation was based on the assumption that 20% of patients who are critically ill have elevated TNF- α levels compared to 5% of patients who are noncritically ill [8]. TNF levels will be normalized according to the study population. Based on a bilateral 95% significance level, a power of 80%, and a case-control ratio of 1, a sample size of 200 patients can be predicted.

Statistical Analysis

Clinical and demographic data between groups of patients (severe vs nonsevere) as well as treatment profiles and differences in successive time points will be compared. To compare mean values of soluble biomarkers between groups, the *t* student test (or analysis of variance with post hoc test for multiple groups) or the nonparametric Mann-Whitney (or Kruskal-Wallis for multiple groups) test will be used as appropriate, according to the observed sample distribution features. The SAS 9.3 software (SAS Institute Inc) will be used with a significance level set at .05. The main binary outcomes will be analyzed by the estimation of relative risks using a log-binomial generalized model or by the area under the curve using trapezoidal methods. All personnel conducting laboratory procedures will be blinded regarding the patient status (severity of COVID-19). Receiver operating characteristic curves will determine cutoff points at which individual or combined scores of the molecular and cellular biomarkers become informative of the progression of COVID-19 cases, according to optimal sensitivity and specificity to identify the signature that best characterizes each clinical status.

Results

This protocol is in the data collection phase. Study recruitment started in June 2020. At the end of July 2020, 30 T-branch and 85 D-branch patients were enrolled.

We expected to complete all patient inclusion by June 2020, but with the continuous increase in COVID-19 cases in Brazil, the authors decided to continue including patients until February 2021.

Data analysis is scheduled to start after all inclusion data have been collected.

The coagulation study branch, with thromboelastometry, has already been completed. Preliminary results confirm deregulation in initiation of the hemostasis process. The results are currently being analyzed and prepared for publication.

Discussion

This TARGET protocol was designed to standardize the evaluation of cellular and molecular immune biomarkers to evaluate their potential as prognosis tools during COVID-19 infection at different degrees of clinical severity. As the host immune response impacts COVID-19 progression, understanding the behavior of immune biomarkers at the different phases of the illness constitutes a crucial step in the identification of patients who will deteriorate and those who will benefit most from treatment. A simultaneous comprehensive assessment of the different aspects of the immune response was the approach adopted for this protocol.

An early study in China showed that the elevation of certain biomarkers such as D-dimer, together with inflammatory markers including ferritin, was associated with the worst outcomes after SARS-CoV-2 infection [33]. These measurements have been incorporated in some clinical practice centers, but their course during disease and actual value in prognosis are not yet fully described. Higher levels of a series of other interleukins were also described in severe forms of the disease [34], contributing to the concept of a cytokine storm, but their exact significance remains unclear. A thorough evaluation of different immune aspects could help to clarify their role.

Less information regarding the cellular immune response has been published, but its role is progressively gaining more attention from the scientific community, as some evidence notes that humoral immunity does not appear to be sufficiently developed after the first SARS-CoV-2 infection [35]. A simultaneous evaluation of these two kinds of immune responses in the TARGET study could help to understand this interface.

Thromboembolism is a recurrent finding among patients with COVID-19, which has made thromboprophylaxis a vital part of the available supportive treatment options. Unfortunately, there is considerable uncertainty about the degree of coagulation derangement, the possible association with the inflammatory response elicited including neutrophil extracellular traps [36], and the consequences of these alterations [13]. Further knowledge is needed to better understand COVID-19-associated coagulopathy to provide frontline clinicians with better treatment options to manage the ensuing clinical manifestations.

A metabolomics study of serum from patients with COVID-19 annotated 941 metabolites. The authors identified metabolic patterns in severe cases that could be used to propose diagnostic models capable of predicting progression to severe infection and assist in the treatment strategy [37]. Observed changes in the lipid profile (>100 lipids) cause liver damage, as reflected by abnormal serum levels of bilirubin and bile acids [37]. Another study revealed the consequences of treating patients with SARS-CoV with methylprednisolone. Disturbances in the serum lipid profile 12 years post infection were associated with long-term systemic damage caused by high doses of methylprednisolone [38]. Metabolomics is therefore a powerful tool for identifying and monitoring the prognosis and markers at different stages of a disease, particularly for unknown infections [24].

Similarly, neutrophil functional and molecular assays have been performed in patients with COVID-19 [39], clearly indicating the participation of these cells in the pathogeny, although no specific molecular model has yet been proposed [40]. Therefore, the proteomic approach coupled with further analysis at the transcription and functional level will provide evidence to correlate neutrophil activity to the disease severity and time course.

Only two treatments have shown substantial beneficial effects to date in randomized trials in COVID-19, with both exhibiting heterogeneity of treatment effect between subgroups. A preliminary report from Beigel et al [41] showed that remdesivir shortened the median recovery in a trial from 15 days in the placebo group to 11 days, but those on mechanical ventilation were less likely to benefit. On the other hand, dexamethasone

demonstrated a reduction in mortality at 28 days, but mainly in those on mechanical ventilation [42]. One possible explanation for these findings is that an adequate immune response to stop viral replication is needed at the onset of the disease. The excess of inflammation presenting is detrimental. As the time when these treatments are initiated could be key, immune biomarkers that signal phases of disease to guide the timing of treatments could be extremely useful in clinical practice.

In summary, TARGET is a translational study that aims to verify the role of cellular and molecular immune biomarkers in the prognosis of COVID-19, opening up avenues for their use in clinical practice. The results that will be achieved are not meant to be restricted to the description of the disease pathophysiology, but to form a basis for future clinical studies that will ultimately help the clinicians on the front line.

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Conflicts of Interest

None declared.

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Abbreviations

- ACE2:** angiotensin converting enzyme-2
CNPq: Conselho Nacional de Desenvolvimento Científico e Tecnológico
D: days of hospitalization
EXTEM: extrinsic system assay
FIBTEM: fibrinogen assay
IFN- γ : interferon-gamma
INTEM: intrinsic system assay
MCP-1: monocyte chemoattractant protein-1
NATEM: nonactivated coagulation assay
PBMC: peripheral blood mononuclear cells
PMA: phorbol 12-myristate 13-acetate
qRT-PCR: quantitative reverse transcription polymerase chain reaction
RECOVERY: Randomised Evaluation of COVID-19 Therapy
RT-PCR: reverse transcription polymerase chain reaction
SARS-CoV: severe acute respiratory syndrome-related coronavirus
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
T: timeline
TNF- α : tumor necrosis factor-alpha
UnB: University of Brasília
UPLC-PDA-QqTOF: ultra-performance liquid chromatography photodiode array quadrupole-quadrupole-time-of-flight
WHO: World Health Organization

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Protocol

Extreme Prematurity and Pulmonary Outcomes Program in Saitama: Protocol for a Prospective Multicenter Cohort Study in Japan

Fumihiko Namba¹, MD, PhD[‡]; Kosuke Tanaka¹, MD, PhD; Sayu Omori², MD; Kazushige Ikeda², MD; Ken Kawabata³, MD, PhD; Hiroaki Sato⁴, MD, PhD; Masakazu Honda⁵, MD, PhD; Tomonori Ichikawa⁶, MD; Yoshihiro Minosaki⁶, MD; Takehiro Michikawa⁷, MD, PhD; Shuntaro Oka¹, MD; Kazuhiko Kabe¹, MD, MMA

¹Department of Pediatrics, Saitama Medical Center, Saitama Medical University, Saitama, Japan

²Division of Neonatology, Department of Pediatrics, Saitama City Hospital, Saitama, Japan

³Division of Neonatology, Saitama Children's Medical Center, Saitama, Japan

⁴Division of Neonatology, Department of Perinatal and Neonatal Medicine, Saitama Medical Center, Jichi Medical University, Saitama, Japan

⁵Division of Neonatal Medicine, Department of Pediatrics, Saitama Medical University Hospital, Saitama, Japan

⁶Neonatal Intensive Care Unit, Kawaguchi Municipal Medical Center, Saitama, Japan

⁷Department of Environmental and Occupational Health, School of Medicine, Toho University, Tokyo, Japan

[‡]The EPOPS Investigators

Corresponding Author:

Fumihiko Namba, MD, PhD

Department of Pediatrics

Saitama Medical Center

Saitama Medical University

1981 Kamoda

Saitama, 350-8550

Japan

Phone: 81 49 228 3727

Fax: 81 49 226 2325

Email: nambaf@saitama-med.ac.jp

Abstract

Background: Because of the improvements in survival rates for preterm infants, not only the rates of bronchopulmonary dysplasia (BPD) but also those of long-term respiratory complications of premature birth are increasing, resulting in financial and health burdens in developed countries. Thus far, the risk factors of respiratory morbidities in extremely preterm infants remain unknown. Furthermore, the definition and the predictive ability of BPD for long-term respiratory outcomes are yet to be determined.

Objective: The objective of our study, Extreme Prematurity and Pulmonary Outcomes Program in Saitama, is to develop the diagnostic criteria for BPD and to determine the prognostic factors contributing to the long-term pulmonary outcomes manifesting in extremely preterm infants.

Methods: The Extreme Prematurity and Pulmonary Outcomes Program in Saitama is an observational prospective cohort study performed by a consortium of six neonatal intensive care units (NICUs) in Saitama, Japan. The subjects included in this study are infants (from each clinical center) with gestational ages 22 to 27 weeks. The target is 400 subjects. This study aims to determine the definition of BPD and other perinatal factors that accurately predict the long-term pulmonary outcomes in survivors of extreme prematurity. Moreover, the association between BPD and postprematurity respiratory disease will be investigated using generalized linear models.

Results: The protocol and consent forms were evaluated and approved on September 5, 2019, by the Ethics Committee of Saitama Medical Center, Saitama Medical University. Enrollment began on April 1, 2020. It is expected to end on March 31, 2023. The follow-up for 1 year corrected age is expected to continue through the middle of 2024.

Conclusions: The Extreme Prematurity and Pulmonary Outcomes Program in Saitama incorporates aspects of neonatal care in secondary- and tertiary-level NICUs to develop existing research studies on the definition of BPD, objective biomarkers, and

outcome measures of respiratory morbidity in extremely preterm infants beyond NICU hospitalization, thereby leading to a novel understanding of the nature and natural history of BPD and potential mechanistic and therapeutic targets in at-risk subjects.

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KEYWORDS

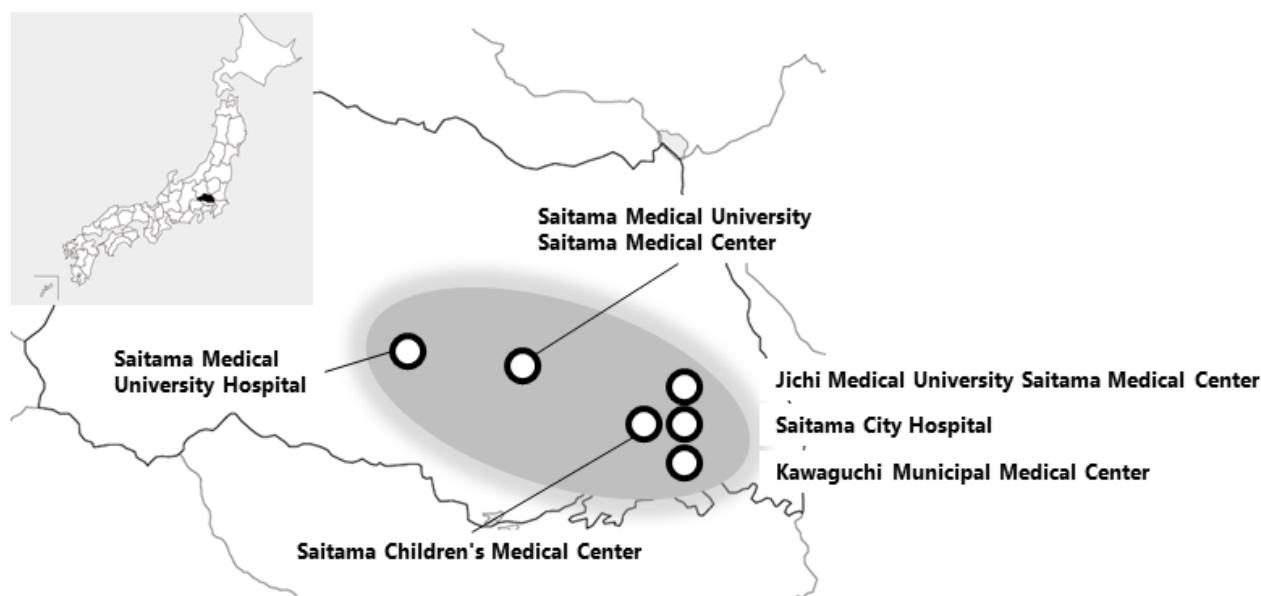
prematurity; preterm infant; bronchopulmonary dysplasia; respiratory outcome

Introduction

The rate of preterm birth has been increasing over the past several decades [1]. Preterm birth is associated with serious respiratory diseases, such as bronchopulmonary dysplasia (BPD), which can be problematic during the first 2 years of life and even in the teen and adult years [2]. Defining the diagnostic criteria for BPD and a better understanding of the etiologies and risk factors of respiratory diseases associated with prematurity, especially BPD, are important to effectively prevent and treat long-term pulmonary morbidities [2]. It is well known that the chance of developing BPD in preterm infants is inversely related to their gestational age. However, other reliable clinical markers to estimate the severity of future disease or predict the likelihood of infants developing long-term respiratory complications are insufficient, and objective biochemical or physiologic indexes for clinical or research purposes are also uncommon. Considering the gaps in definitional, operational, and mechanistic understanding, Maitre et al created the Prematurity and Respiratory Outcomes Program (PROP), a prospective multicenter study of respiratory outcomes among preterm infants in the United States, with the goal to determine

the characteristics of persistent pulmonary diseases associated with prematurity and develop the means of predicting the risk factors of the disease [3,4]. They concluded that both BPD and perinatal clinical data, including male sex, smoking during pregnancy, infant race, public insurance, birth weight, and parent with asthma, accurately determined extremely preterm infants at risk for persistent and severe respiratory morbidity at 1 year [5]. However, the definition and predictive ability of BPD regarding long-term respiratory outcomes are yet to be determined [6,7]. Therefore, we created the Extreme Prematurity and Pulmonary Outcomes Program in Saitama to determine the diagnostic criteria for BPD and the prognostic factors contributing to the 1-year respiratory morbidity in a cohort of more than 400 extremely preterm infants. The Extreme Prematurity and Pulmonary Outcomes Program in Saitama will be implemented in six neonatal intensive care units (NICUs), including two tertiary-level and four secondary-level NICUs, located in Saitama, Japan (Figure 1). The data collected from the Extreme Prematurity and Pulmonary Outcomes Program in Saitama will also be used to produce a high-resolution phenotype of the disease, which can be used clinically, especially in future clinical trials.

Figure 1. Centers participating in the study. The map has been taken from <https://n.freemap.jp/>. The copyright belongs to FN.



The study protocol shows the design of the Extreme Prematurity and Pulmonary Outcomes Program in Saitama study and the breadth of data that will be obtained throughout the NICU stay and 1-year follow-up period. In this study, we aim to develop the diagnostic criteria for BPD and to determine the prognostic

factors contributing to the long-term pulmonary outcomes manifesting in extremely preterm infants.

Methods

Participating Centers and Their Roles and Responsibilities

The Extreme Prematurity and Pulmonary Outcomes Program in Saitama required each participating center to follow a multisite shared protocol for measuring the respiratory phenotypes and outcomes of extremely preterm infants. A total of five NICUs (three secondary-level and two tertiary-level NICUs) monitor the activities of all extremely preterm infants (<28 weeks) born in Saitama, Japan (Figure 1), and each NICU contributes to the data collection, coordination, and oversight of the multicenter components. Saitama Medical Center, Saitama Medical University manages the clinical report forms, provides support for the standardization of definitions and data collection, identifies and resolves issues, encourages the other participating NICUs to report updates of the project, and determines the necessary steps to be taken by the NICUs. The Extreme Prematurity and Pulmonary Outcomes Program in Saitama working group developed the initial protocols for maternal and neonatal database elements (Multimedia Appendix 1, Multimedia Appendix 2, Multimedia Appendix 3, Multimedia Appendix 4, and Multimedia Appendix 5) and consulted about the protocol of the PROP study regarding respiratory measurements, such as the oxygen requirement challenge test [4].

Multicenter Protocol Development

Primary and Secondary Outcomes

The aims of the Extreme Prematurity and Pulmonary Outcomes Program in Saitama are to determine the definition of BPD and

to identify early clinical, physiological, or biochemical biomarkers during the NICU hospitalization, which are deemed to predict respiratory morbidity throughout the first year of life. The primary outcome observed by the Extreme Prematurity and Pulmonary Outcomes Program in Saitama is the presence or absence of postprematurity respiratory disease (PRD), a composite outcome that will be obtained from longitudinal data in the first year after discharge from the NICU [4]. Morbidity in the following four domains will be examined: (1) respiratory symptoms; (2) medication use; (3) hospitalizations; and (4) dependence on technology during the first year of life. Mortality from a cardiorespiratory cause will be considered as well.

Secondary outcomes include respiratory morbidity severity [5], premature infant respiratory status, chronic respiratory morbidity (CRM) 1, CRM 2, death, neurodevelopmental outcomes, visual and hearing impairments, time to final weaning off from oxygen therapy, and time to final weaning off from respiratory technology support.

Protocol

The inclusion and exclusion criteria are listed in Textbox 1, and the protocol is outlined in Figure 2. The sample size for this multicenter cohort study is prespecified to include 400 extremely preterm infants at the birth time point (280 [70%] infants with BPD and 120 [30%] infants without BPD, based on our previous study [8]). The difference in PRD occurrence between BPD and non-BPD patients will be compared. This sample size has a statistical power of 80% to detect a difference in PRD occurrence between BPD and non-BPD patients (PRD occurrence is roughly 80% in BPD patients and 60% in non-BPD patients, based on the PROP study [5]).

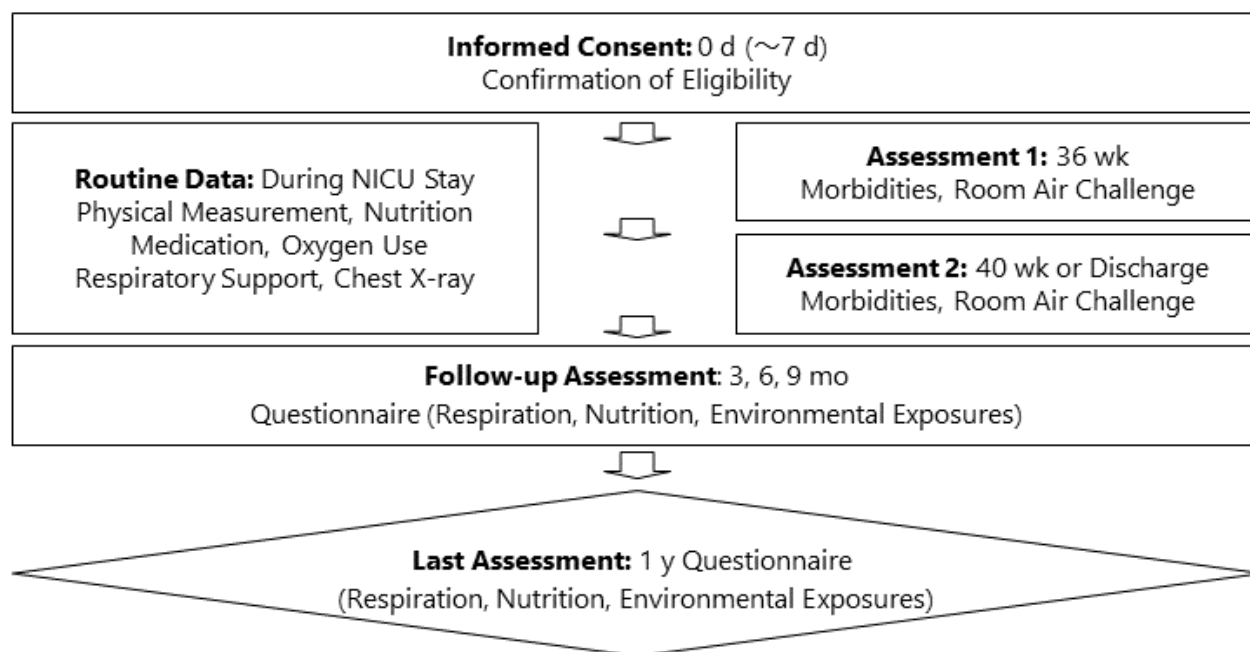
Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Informed consent obtained and consent form signed
- 7 days of age or less at enrollment
- 22 0/7 to 27 6/7 weeks using the best obstetrical estimate

Exclusion criteria

- Structurally significant congenital heart disease
- Structural abnormalities of the upper airway, lung, or chest wall
- Congenital malformation or syndrome that adversely affects life expectancy or cardiopulmonary development
- Family unlikely to be available for long-term follow-up
- Considered by the investigator to be an unsuitable candidate for this study

Figure 2. Protocol outline. NICU: neonatal intensive care unit.

Clinical Data Collection, Management, and Storage Systems

All data are prospectively collected from birth through medical record reviews and family interviews, and include maternal and infant demographics; clinical data and comorbidities; and daily infant respiratory, nutritional, and medication data throughout the NICU stay (Multimedia Appendix 1, Multimedia Appendix 2, Multimedia Appendix 3, Multimedia Appendix 4, and Multimedia Appendix 5). After discharge from the NICU, a series of questionnaires, in accordance with that of the PROP study [4], is used. The questionnaires assess the domains of respiratory morbidity at 3, 6, 9, and 12 months corrected age. At 6 and 12 months, a survey on environmental respiratory irritant exposures, including tobacco smoke and animal substances, is conducted as well. An in-person visit for physical examination and history taking is performed at 1 year corrected age.

NICUs contribute and retain access to their own data through an electronic data capture software (NICU Data Management System [NDMS], Education Software Co, Ltd). In each NICU, all the data, without identifying personal information, are exported to a CSV file, and the file is sent to Saitama Medical Center, Saitama Medical University.

Assessments of Physiological Room-Air Challenge

To physiologically define and classify BPD, data regarding the requirement of supplemental oxygen estimated by the standardized oxygen requirement challenge test at 36 weeks postmenstrual age (PMA) and at 40 weeks PMA or discharge (whichever comes first) are collected. The protocol developed by Walsh et al [9] was modified to effectively discriminate between the effects of FiO_2 and flow [4] (Multimedia Appendix 6).

Analytical Approaches

The subjects are classified into the following two groups: BPD and non-BPD. Concerning the maternal and neonatal background information, the frequency and percentage in each group are calculated for discrete data, whereas descriptive statistic values in each group, such as mean and SD, and median and IQR, are calculated for continuous data.

The primary outcome of PRD requires that infants demonstrate pulmonary morbidity in one of the following four domains that are examined after discharge from the NICU: (1) respiratory medications; (2) hospitalization from a cardiopulmonary cause; (3) coughing, wheezing, or other respiratory symptoms; and (4) home technology dependence in at least two time frames (at 3-month intervals) during the first year of life. Death from a respiratory cause is also included. We will apply generalized linear models to treat repeated measures and check the statistical difference in the PRD incidence in the presence and absence of BPD after adjustment for several covariates. Gestational age and variables with a P value $<.05$ in univariate analyses will be considered for inclusion in multivariate models. Missing values are not complemented, because the number of cases of missing values is extremely small. When the outliers other than abnormal values with apparent causes are excluded, their handling procedure is determined by blind review of the data, and the statistical analysis plan is revised.

To analyze the potential influence of gestational age on respiratory outcomes, a subgroup analysis will be conducted. Based on the gestational age at birth, the subjects will be divided into the following three subgroups: (1) 22 and 23 weeks of gestation, (2) 24 and 25 weeks of gestation, and (3) 26 and 27 weeks of gestation.

Study Approval by Institutional Review Boards

The multicenter Extreme Prematurity and Pulmonary Outcomes Program in Saitama protocol and consent forms were evaluated

by the Ethics Committee of Saitama Medical Center, Saitama Medical University (initial approval date: September 5, 2019). In addition, the institutional review board at each Extreme Prematurity and Pulmonary Outcomes Program in Saitama site determined the risk level, based on local interpretation. The complete list of institutional review board approvals and protocol numbers can be found in [Multimedia Appendix 7](#).

Patient and Public Involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Results

Written informed consent will be obtained from the parents of the infants enrolled in this study. Enrollment began on April 1, 2020, in Saitama Medical Center, Saitama Medical University, and May 1, 2020, in the other NICUs. It is expected to end on March 31, 2023. The follow-up for 1 year corrected age is expected to continue through the middle of 2024. Four and eight eligible extremely preterm infants were enrolled in April and May 2020, respectively.

Discussion

We are conducting a prospective multicenter cohort study to develop the diagnostic criteria for BPD and to determine the

prognostic factors contributing to the long-term pulmonary outcomes manifesting in extremely preterm infants. The definition of BPD has gradually evolved, since the initial description of the disease in 1967 by Northway et al [10]. Shennan et al suggested the definition of supplemental oxygen requirements at 36 weeks PMA [11]. In 2000, the severity-based definition, which categorizes BPD as mild, moderate, or severe according to the respiratory support provided at 36 weeks PMA among very preterm infants treated with supplemental oxygen for at least 28 days, was constructed (NIH consensus definition) [12]. However, the validity and utility of these commonly used definitions have been questioned, because it has been reported that (1) there is an inconsistent correlation with long-term respiratory outcomes [13], (2) oxygen/respiratory support at 40 weeks, not at 36 weeks, is the best predictor for serious respiratory morbidity [7], and (3) regardless of supplemental oxygen use, respiratory support at 36 weeks PMA best predicted early childhood morbidity [6]. Therefore, the Extreme Prematurity and Pulmonary Outcomes Program in Saitama, a prospective multicenter cohort study of extremely preterm infants in Japan, will be conducted in order to provide a novel definition of BPD that can best predict the long-term pulmonary outcomes throughout the first year of life and a better understanding of the mechanisms, evolution, and consequences of lung diseases among extremely preterm infants.

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Authors' Contributions

FN was responsible for this paper. FN, KT, and TM made substantial contributions to study design, coordination, manuscript drafting, and manuscript revision for intellectual content. TM made substantial contributions to the statistics. SOMori, KI, KKawabata, HS, MH, TI, YM, SOka, and KKabe conceived significant portions of the study, made intellectual contribution to the study protocol, and read and edited the manuscript. All authors read and approved the final manuscript. The Extreme Prematurity and Pulmonary Outcomes Program in Saitama investigators contributed to the design of the multicenter study.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Extreme Prematurity and Pulmonary Outcomes Program in Saitama: baby's baseline data.

[\[DOCX File, 36 KB - resprot_v10i3e22948_app1.docx\]](#)

Multimedia Appendix 2

Extreme Prematurity and Pulmonary Outcomes Program in Saitama: daily growth and nutrition/daily medication data.

[[DOCX File , 29 KB - resprot_v10i3e22948_app2.docx](#)]

Multimedia Appendix 3

Extreme Prematurity and Pulmonary Outcomes Program in Saitama: comorbidities of prematurity.

[[DOCX File , 35 KB - resprot_v10i3e22948_app3.docx](#)]

Multimedia Appendix 4

Extreme Prematurity and Pulmonary Outcomes Program in Saitama: standard Visit.

[[DOCX File , 29 KB - resprot_v10i3e22948_app4.docx](#)]

Multimedia Appendix 5

Extreme Prematurity and Pulmonary Outcomes Program in Saitama: brain imaging data.

[[DOCX File , 22 KB - resprot_v10i3e22948_app5.docx](#)]

Multimedia Appendix 6

Oxygen requirement challenge test.

[[DOCX File , 13 KB - resprot_v10i3e22948_app6.docx](#)]

Multimedia Appendix 7

Institutional review board protocols at individual Extreme Prematurity and Pulmonary Outcomes Program in Saitama sites.

[[DOCX File , 16 KB - resprot_v10i3e22948_app7.docx](#)]

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Abbreviations

BPD: bronchopulmonary dysplasia

CRM: chronic respiratory morbidity

NICU: neonatal intensive care unit

PMA: postmenstrual age

PRD: postprematurity respiratory disease

PROP: Prematurity and Respiratory Outcomes Program

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Protocol

Modeling Risk Factors for Sleep- and Adiposity-Related Cardiometabolic Disease: Protocol for the Short Sleep Undermines Cardiometabolic Health (SLUMBRx) Observational Study

Adam P Knowlden¹, MBA, MS, PhD; John C Higginbotham^{2*}, PhD; Michael A Grandner^{3*}, PhD; John P Allegrante^{4,5*}, PhD

¹Department of Health Science, College of Human Environmental Sciences, The University of Alabama, Tuscaloosa, AL, United States

²Department of Community Medicine and Population Health, College of Community Health Sciences, The University of Alabama, Tuscaloosa, AL, United States

³Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ, United States

⁴Department of Health and Behavior Studies, Teachers College, Columbia University, New York, NY, United States

⁵Department of Sociomedical Sciences, Mailman School of Public Health, Columbia University, New York, NY, United States

*these authors contributed equally

Corresponding Author:

Adam P Knowlden, MBA, MS, PhD
Department of Health Science
College of Human Environmental Sciences
The University of Alabama
Russell Hall 104
Box 870313
Tuscaloosa, AL, 35487
United States
Phone: 1 205 650 9026
Email: aknowlden@ches.ua.edu

Abstract

Background: Obesity and short sleep duration are significant public health issues. Current evidence suggests that these conditions are associated with cardiovascular disease, metabolic syndrome, inflammation, and premature mortality. Increased interest in the potential link between obesity and short sleep duration, and its health consequences, has been driven by the apparent parallel increase in the prevalence of both conditions in recent decades, their overlapping association with cardiometabolic outcomes, and the potential causal connection between the two health issues. The SLUMBRx (Short Sleep Undermines Cardiometabolic Health) study seeks to contribute to the development of a comprehensive adiposity-sleep model while laying the groundwork for a future research program that will be designed to prevent and treat adiposity- and sleep-related cardiometabolic disease risk factors.

Objective: This SLUMBRx study aims to address 4 topics pertinent to the adiposity-sleep hypothesis: the relationship between adiposity and sleep duration; sex-based differences in the relationship between adiposity and sleep duration; the influence of adiposity indices and sleep duration on cardiometabolic outcomes; and the role of socioecological factors as effect modifiers in the relationship between adiposity indices, sleep, and cardiometabolic outcomes.

Methods: SLUMBRx will employ a large-scale survey (n=1000), recruiting 159 participants (53 normal weight, 53 overweight, and 53 obese) to be assessed in 2 phases.

Results: SLUMBRx was funded by the National Institutes of Health, Heart, Lung, and Blood Institute through a K01 grant award mechanism (1K01HL145128-01A1) on July 23, 2019. Institutional Review Board (IRB) approval for the research project was sought and obtained on July 10, 2019. Phase 1 of SLUMBRx, the laboratory-based component of the study, will gather objective adiposity indices (air displacement plethysmography and anthropometrics) and cardiometabolic data (blood pressure, pulse wave velocity and pulse wave analysis, and a blood-based biomarker). Phase 2 of SLUMBRx, a 1-week, home-based component of the study, will gather sleep-related data (home sleep testing or sleep apnea, actigraphy, and sleep diaries). During phase 2, detailed demographic and socioecological data will be collected to contextualize hypothesized adiposity and sleep-associated cardiometabolic disease risk factors. Collection and analyses of these data will yield information necessary to customize future observational and intervention research.

Conclusions: Precise implementation of the SLUMBRx protocol promises to provide objective and empirical data on the interaction between body composition and sleep duration. The hypotheses that will be tested by SLUMBRx are important for understanding the pathogenesis of cardiometabolic disease and for developing future public health interventions to prevent its conception and treat its consequences.

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KEYWORDS

abdominal obesity-metabolic syndrome; adiposity; body composition; body fat distribution; insufficient sleep syndrome; observational study; short sleeper syndrome; sleep deprivation

Introduction

Background

Obesity and short sleep in adults are highly prevalent in the United States [1]. Both conditions are associated with numerous adverse health outcomes, including all-cause mortality [2], cardiovascular disease [3], diabetes [4], metabolic syndrome [5], inflammation [6], and psychiatric disorders [7]. Approximately 38% of adults in the United States are classified as obese, with a BMI of 30 kg/m² or greater [8]. Stratified by sex, 35.2% of men and 40.5% of women meet the BMI cutoff point for obesity [8]. Similarly, short sleep is common, with an estimated 35.3% of adults in the United States receiving less than the recommended 7 hours of sleep during a 24-hour period [9]. Among this sample, 56.5% of men and 39.6% of women self-reported snoring [9], a symptom associated with sleep-disordered breathing [10]. Of increasing importance is the relationship between short sleep, obesity, and cardiometabolic outcomes [11,12]; nevertheless, little is known about these associations [13] or how public health interventions can be applied to prevent and treat adiposity and sleep-associated cardiometabolic disease risk factors [14].

Although progress has been made in modeling the relationship between sleep and adiposity, much work remains [15,16]. The data from the epidemiological and experimental studies of obesity and short sleep, although suggestive, need to be viewed within context. Epidemiological studies frequently have several methodological limitations, including being (1) retrospective, (2) cross-sectional, and (3) based on self-reported data [17]. Often, (4) nonvalidated measures [9] are used along with (5) inconsistent definitions of short sleep (eg, 6 [18] to 9 [19] hours). In addition, such studies have (6) limited control over potential confounding variables [20] and (7) report inconsistent modeling of sleep as a cause or consequence of obesity [21]. Taken together, these limitations often lead to mixed results. Moreover, they limit the ability to evaluate causal models linking adiposity and sleep duration, thereby precluding the capacity to posit sleep as a modifiable risk factor for the treatment of overweight and obesity.

Concurrently, experimental studies often rely on (1) small sample sizes [22] combined with (2) terse periods of observation [23] (3) in rigorously controlled settings (potentially eliciting Hawthorne effects [24]), and (4) the suppression of one or more

free-living factors hypothesized to influence the relationship between adiposity and sleep (eg, prohibiting exercise [25]). Although experimental studies are methodologically rigorous and suggestive of a causal connection between adiposity and sleep, the design features often limit translation to free-living populations.

The SLUMBRx (Short Sleep Undermines Cardiometabolic Health) study will capitalize on the strengths of the literature and attempt to address salient limitations. The methods and findings from the epidemiological literature will be considered by using a standardized survey approach to provide a theoretical backdrop against which to contextualize results. The findings and methods from the experimental literature will be incorporated by collecting objective measures of adiposity, sleep, and cardiometabolic outcomes. Therefore, the proposed SLUMBRx research study can assist in filling important gaps in our understanding of the relationship between these health outcomes.

Overarching Aim of the Proposed Research

The overarching aim of the SLUMBRx study is to acquire a more comprehensive understanding of the relationship among adiposity, short sleep, and cardiometabolic risk factors (Table 1). The relationship between adiposity and sleep duration will be investigated to facilitate the primary aim of the SLUMBRx study. First, although studies have identified associations between obesity and short sleep in adults, there are occasional inconsistencies in research findings, with some studies observing an inverse linear relationship, U-shaped association, or no significant relationship [15,26,27]. Second, sex-based differences in the relationship between adiposity and sleep will be evaluated. Studies within this domain have identified interesting, yet often, inconsistent findings [25,28-31]. However, few studies have examined sex-based variations in adiposity and sleep duration using rigorous measures of adiposity [25,28-31]. Third, the association between adiposity and sleep on cardiometabolic outcomes requires further investigation, particularly considering updated blood pressure guidelines [32]. Fourth, adiposity, sleep, and cardiometabolic outcomes are influenced by a myriad of upstream and downstream factors [33]. Contextualizing the adiposity-sleep connection from a socioecological perspective [34] is crucial to understanding the full scope of their relationship and impact on cardiometabolic disease.

Table 1. Hypotheses and methods of analysis.

Hypothesis	Method of analysis
Hypothesis 1: participants who are overweight and obese will demonstrate significantly shorter sleep relative to participants classified as normal weight	Analysis 1: continuous outcome sleep hours will be evaluated using a one-way ANOVA ^a for BMI (3 levels: normal, overweight, and obese)
Hypothesis 2: male and female participants will demonstrate significantly different adiposity effects on sleep duration outcomes	Analysis 2: continuous outcome sleep hours will be evaluated using factorial ANOVA. The interaction effects between sex (2 levels: male and female) and BMI (3 levels: normal, overweight, and obese) will be examined
Hypothesis 3: participants who are overweight and obese will exhibit greater cardiometabolic risk outcomes compared with those who are normal weight; this relationship will be stronger in participants who are overweight and obese with short sleep duration	Analysis 3: continuous cardiometabolic risk factors are dependent variables. Sleep (2 levels: short and normal) and BMI (3 levels: normal, overweight, and obese) are independent variables. Factorial ANOVA will be used to evaluate the interaction effects as well as simple effects of sleep and obesity on cardiometabolic risk factors
Exploratory specific aim 4: to explore the role of socioecological factors (societal, social, and individual levels) as effect modifiers in the relationship between adiposity indices, sleep, and cardiometabolic outcomes. No formal hypothesis testing will occur for specific aim 4, because of sample size limitations	Analysis 4: descriptive statistics will provide important information regarding the impact of socioecological variables on sleep. Linear mixed models will be used to examine multilevel effects. Sleep hours is the dependent variable. Cardiometabolic (cardio), obesity, social, and societal factors are the independent variables

^aANOVA: analysis of variance.

Specific Aims and Hypotheses

A community sample (N=160) of participants who are normal weight, overweight, and obese will be invited to participate in the proposed SLUMBRx study to accomplish these goals. Phase 1 of SLUMBRx will include measurement of adiposity indices and cardiometabolic outcomes in a clinical setting. Phase 2 of SLUMBRx will include sleep apnea screening and 1 week of daily sleep diaries and actigraphy using epidemiological data collection techniques. During phase 2, participants completed a set of validated questionnaires examining sociodemographic factors associated with adiposity indices, sleep disorders, and cardiometabolic outcomes.

Objective measures of adiposity indices, sleep outcomes, and cardiometabolic predictors will be collected from participants over the course of the SLUMBRx study. Specific measures will include the following:

- Adiposity indices: anthropometrics (BMI, skinfold thicknesses, and circumferences) [35,36] and air displacement plethysmography [37].
- Cardiometabolic predictors: blood pressure [38], pulse wave velocity and pulse wave analysis [39,40], and blood-based biomarkers [41].
- Sleep outcomes: home sleep testing or sleep apnea [42,43], sleep diaries [44], and actigraphy [45].

In addition to clinical outcomes, sex-based differences in the relationship between adiposity and sleep duration will be investigated [25,28-31]. This study will also assess socioecological factors [33] that influence adiposity indices, sleep, and cardiometabolic outcomes as an exploratory aim.

- Specific aim 1: to determine the relationship between adiposity and sleep duration.
 - Hypothesis 1: participants who are overweight and obese will demonstrate significantly shorter sleep than participants classified as normal weight.
- Specific aim 2: to evaluate sex-based differences in the relationship between adiposity and sleep duration.

- Hypothesis 2: male and female participants will demonstrate significantly different adiposity effects on sleep duration outcomes.
- Specific aim 3: to assess whether adiposity and sleep duration influence cardiometabolic outcomes.
 - Hypothesis 3: participants who are overweight and obese will exhibit greater cardiometabolic risk outcomes compared with participants who are of normal weight; this relationship will be stronger in participants who are overweight and obese with short sleep duration.
- Specific aim 4 (exploratory): to explore the role of socioecological factors as effect modifiers in the relationship between adiposity, sleep, and cardiometabolic outcomes.
 - Owing to sample size limitations, formal hypothesis testing will not occur for aim 4.

Methods

Sample Size Considerations

Power analyses for testing the SLUMBRx hypotheses were calculated [46] using an α of .05 and effect sizes that would yield a power of 0.80. Sample size estimates were primarily based on detecting significance for *specific aim 1*. Data from the 2007 to 2008 National Health and Nutrition Examination Survey (NHANES) [47] were used to estimate the power analysis parameters. Analysis of NHANES data revealed that mean sleep hours were 7.08 (SD 1.3) hours for individuals who are normal weight, 6.84 (SD 1.3) hours for individuals who are overweight, and 6.72 (SD 1.3) hours for individuals who are obese. Although NHANES data were based on self-reports, the SLUMBRx study will apply validated sleep diaries and objective sleep measures (accelerometers). Therefore, the means and SDs for the proposed SLUMBRx study would likely be smaller than those of NHANES. Applying an SD of 0.60 with the same mean values of sleep duration as NHANES for the 3 groups, 53 participants per group are required to achieve a power of 0.80, with an effect size of 0.25 for a total sample size of 159

participants for *specific aim 1*. Similar sample sizes are required for the remaining specific aims. For example, using the same parameters, *specific aim 2* requires a sample size of 52 participants per group (156 total) to detect significant adiposity by sex interaction (0.26 effect size). A total of 160 participants will be recruited to accommodate specific aims 1 to 3.

A power analysis was not conducted for *exploratory specific aim 4*. Given that this is the first attempt at building a socioecological model of sleep, limited information is available to specify sample size parameters. Although formal hypothesis testing will not be conducted for *specific aim 4*, it is expected that the descriptive statistics and multilevel model will provide

important information regarding the impact of socioecological variables on sleep. There has been a continuous call for the inclusion of socioecological models in public health, as these models can provide a more comprehensive context to understand sleep [48].

Inclusion and Exclusion Criteria

Inclusion criteria will limit SLUMBRx study eligibility to (1) adults, 18 years of age or older, (2) with reliable internet access, email, and telephone, and (3) a commitment to completing all study activities. Exclusion criteria for the SLUMBRx study are described in [Textbox 1](#).

Textbox 1. Exclusion criteria for the SLUMBRx (Short Sleep Undermines Cardiometabolic Health) study.

- Participants must be willing to commit to the SLUMBRx protocol, which includes air displacement plethysmography, pulse wave velocity and analysis, collection of blood-based biomarkers, home sleep testing, and completion of questionnaires. Commitment will be assessed during the informed consent process to help ensure compliance and reduce study dropout.
- Unstable medical or psychological distress will be assessed using the Systematic Assessment for Treatment Emergent Events [49,50] questionnaire and the Kessler-6 Psychological Distress Scale [51] to help deter confoundment of lab-based assessments.
- Current medical interventions and medications will be assessed through self-report. Medical interventions via prescription medications (eg, statins) and treatment devices (eg, continuous positive airway pressure therapy) may confound the relationship between adiposity, sleep, and cardiometabolic disease. Similar approaches have been used in other research protocols [52].
- Evidence of substance abuse will be assessed by the CAGE (cut-annoyed-guilty-eye)-Adapted to Include Drugs [53] to help deter confoundment of lab-based assessments
- Pregnancy will be assessed by self-report to help ensure the fetus is not exposed to the procedures involved with the study and ensure the biopsychosocial changes that occur with pregnancy do not confound the lab-based assessments.
- Inadequate language comprehension will be assessed during the intake portion of the lab-based assessment to assure the quality of self-report data, as all the measures are in English
- Lack of return addresses will be assessed through self-report by asking potential participants to provide their mailing address. Data collection tools, such as sleep apnea home-testing kits, must be returned upon use. As such, a return mailing address is required.
- Self-report data will primarily be collected through the web-based data portal; therefore, reliable internet access is required. An email address and phone number are required to communicate with patients if they have any questions about the study and schedule the study's lab-based component.
- Underweight BMI will be assessed by calculating self-reported height and weight. Although underweight BMI is an important variable [54], budgetary constraints will prevent studying this issue for this proposal.
- Long sleep, defined as habitual sleep greater than 9 out of 24 hours [55], will be assessed using item 4 from the Pittsburgh Sleep Quality Index [56]. Long sleep is a proposed risk factor for obesity and cardiometabolic disease. However, long sleep likely interacts with obesity and cardiometabolic disease through unique mechanisms [57]. These issues, combined with budgetary constraints, informed the decision to exclude participants who are underweight from this study.

For screening purposes, BMI [35] will be calculated from self-reported height or weight. Although BMI will be recalculated in a clinical setting during phase 1 of this study, it is anticipated that measurement error associated with self-reported height and weight for BMI calculations will be acceptable for screening and initial group allocation purposes (normal weight, overweight, and obese). Demographic data will also be collected (eg, sex, age, race, or ethnicity) along with a request for a commitment to study completion. Filler items will be included in the screening survey to rule out professional participants. Consent will be obtained for the screening data.

Inclusion of Children, Minorities, and Women

Children will not be included in the SLUMBRx study. Although childhood obesity and poor sleep in children are critical health concerns [58], the aims of SLUMBRx pertain specifically to adults. Risk factors for short sleep and obesity in children appear

to operate differently than those underlying adult obesity and poor sleep [59]. Regarding minority enrollment, there will be an equal opportunity for members of all ethnic and racial backgrounds to participate in the SLUMBRx study. Study design and recruitment are expected to ensure that minorities are well represented. On the basis of the United States Census Bureau's 2016 population estimates for Tuscaloosa [60], we expect our sample to reflect the following racial and minority representation: 65.1% White, 31.8% African American or Black, 1.5% Asian, 0.3% American Indian or Alaskan Native, and 0.1% Native Hawaiian or Pacific Islander. This area's ethnic distribution is 3.5% Hispanic or Latino and 62.1% White alone, not Hispanic or Latino. Recruitment prioritizes a representative minority sample for this metropolitan area. Minority inclusion will be closely monitored during recruitment to ensure adequate representation. Prioritized recruitment of minority groups will be utilized should all groups be underrepresented.

Specific aim 2 of the SLUMBRx study is particularly focused on investigating sex-based differences in the relationship between adiposity and sleep duration. Therefore, the inclusion of women is paramount to the success of this proposal. Multiple studies suggest that women are at higher risk for obesity from short sleep than men [28,61,62]. Other studies have found that men with short sleep are at greater risk for obesity than women [25,29,30]. Ford et al [31] found that sleep duration was associated with BMI; however, there was no evidence of a statistical interaction by gender, race, or ethnicity.

Possible Risks and Benefits to Participants

Risks

The risk to participants is expected to be minimal, as there are minimal risks associated with the completion of the web-based screening survey. Participants will be informed that they may withdraw from the SLUMBRx study at any time if they experience discomfort. Regarding air displacement plethysmography, mild discomfort because of the small dimensions of the chamber is possible. Participants who experience distress will be referred for appropriate treatment. There is minimal risk associated with the pulse wave velocity device as it is applied externally and is noninvasive. In terms of the blood draw, infection, bruising, fainting, and a small amount of bleeding are possible. As participants will be in a fasted state, there are some associated health risks, including dizziness, decreased alertness, and symptoms associated with low blood sugar levels. A qualified phlebotomist will draw blood following standard procedures. In the event that the participants have an adverse reaction to any of the medical procedures, the proximity of the clinical setting where SLUMBRx will transpire to proximity to the local hospital will permit rapid access to emergency response teams. Regarding the home sleep testing kit, mild discomfort from wearing the equipment is possible. To minimize risk, participants will be given a demonstration regarding the setup of the device and oral and illustrated instructions. In addition, a 24-hour contact number to call for any problems will be provided. Similarly, mild discomfort from wearing the blood pressure cuff is possible. To help offset risk, arm circumference will be measured to ensure an appropriate cuff size. There are minimal risks associated with the completion of the web-based screening survey. The primary risk pertains to confidentiality rather than safety risks. All participants will be assigned a study ID. Study ID numbers will be used in all documents for review, evaluation, and analysis. No verbal or written information concerning participants will be released without written consent from the subject. Publication of all results will maintain participant confidentiality. Only group data will be reported. Data will be stored under double-locked conditions and made available only to qualified staff working directly on the project.

Benefits

Participants may gain satisfaction knowing they contributed to a scientific study that may someday result in better diagnostic and treatment options for adiposity, sleep, and cardiometabolic risk factors. Participants will undergo health screening related to their body composition and sleep and be referred to a local sleep clinic if they have any medical questions or concerns.

They will also be provided with a financial incentive and receive free food and drink during the conclusion of the lab-based portion of the study. All participants who complete the full study will be paid US \$100.00; payment will be prorated as follows: US \$40.00 for the lab-based component of the study (phase 1) and US \$40.00 for the home-based component of the study (phase 2). A US \$20.00 bonus will supplement the compensation for participants that provide complete data. However, the primary benefit for eligible participants will be access to health screening services.

Results

Recruitment

A community sample (N=160) of participants who are normal weight, overweight, and obese living in the city of Tuscaloosa, Alabama, will be invited to participate in the SLUMBRx study. Strategies for directing potential participants to the study include posting announcements to web-based classifiers, distribution of informational flyers or brochures throughout the community, including community centers (Tuscaloosa County Park and Recreation Authority), and churches, ads in minority papers (eg, Mobile Beacon and Alabama Citizen), and poster advertisements on the city commuter system (Tuscaloosa Transit Authority). Research study advertising networks established by the University of Alabama Strategic Communications department will also be used. Specific procedures will be employed to maximize our outreach to minority communities and aggregate an ethnically diverse and representative sample, such as targeted advertising, posting in places that serve minority populations, and working with local clergy. In addition to standard advertisement strategies, the study will also be advertised through the University of Alabama media and the established research networking channels developed and fostered by the University of Alabama Institute for Rural Health Research. Each advertisement medium will direct respondents to the main study page.

With these plans, modest recruitment targets, and the Tuscaloosa community's size (population 99,543), it is anticipated that recruitment will be accomplished in a timely manner.

Census data [63] indicate that the crude prevalence of obesity for Tuscaloosa is 41.4%. Panel 3 provides model-based estimates of sleeping less than 7 hours among adults aged 18 years and older living in Tuscaloosa. Census data also indicate that the crude prevalence of short sleep for Tuscaloosa is 46.1%.

Respondents will be able to access the main study page and screening survey through a variety of entry points. For example, flyers will have removable tabs that provide the study page URL, which respondents may tear off and store on their personal computer. In addition to listing the website URL, paper mediums (eg, flyers) will include a quick response code, allowing respondents to access the study's welcome page using their phone camera. The welcome page will provide a basic orientation for the study. If the subject is interested in participating in the study, they will be directed to click on the *I agree* button located at the bottom of the welcome screen. By clicking *I agree*, respondents will be directed to read and

complete 2 informed consent documents, one related to the study and the other related to the Health Insurance Portability and Accountability Act (HIPAA). Once these are read, if the respondent wishes to continue in the study, they must agree to the stipulations of the study consent form and HIPAA documents by clicking on *I agree* button located at the bottom of the page. The informed consent documents will be protected by a content validation algorithm, ensuring that participants cannot proceed to the screening survey without first providing consent. Completing the consent documents initiates the assignment of a study ID, recording of the date and time, and administration of the screening survey. The screening survey will also capture general information such as the respondents' names, mailing addresses, phone numbers, email, and demographic information.

Screening

Eligibility for the SLUMBRx study will be determined by screening with standardized scales and questionnaires. This component of the study will allow for the profiling of participants in a manner that is consistent with large-scale surveys undertaken with epidemiological research. All potential participants may respond to the screening survey. BMI will be calculated using respondents' self-reported height and weight, calculated as $\text{weight}/\text{height}^2$ (expressed as kg/m^2) [8]. Although BMI will be recalculated under controlled conditions during phase 1 of the study, we anticipate measurement error associated with self-reported height and weight for BMI calculations acceptable for screening purposes. On the basis of BMI, participants invited into the study will be (by self-report) of normal weight (BMI 18.5 to <25.0), overweight (BMI 25.0 to <30.0), or obese (BMI ≥ 30.0). For the purposes of this study, participants categorized as underweight (BMI <18.5) will be excluded from participating. Researchers have proposed different mechanisms (eg, eating disorders [54]) may be responsible for the sleep outcomes observed in this group. These issues, combined with budgetary constraints, informed the decision to exclude participants who are underweight from this study.

Following the completion of the screening survey, responses will be reviewed to determine eligibility for the SLUMBRx study. Eligibility was determined using the inclusion or exclusion criteria. As this study sought equivalent sample sizes for the 3 groups being investigated (normal weight, overweight, and obese), once a particular group has reached saturation (determined by calculating BMI from self-reported height and weight), respondents falling into a saturated group will be ineligible to participate in the study. Respondents meeting the study criteria will be contacted to establish a convenient date or time for initiation of the study's laboratory-based portion. Participants will also be made a temporary parking pass to grant them convenient access to the Nutrition and Metabolism Research Lab.

Consent Process

Potential participants will be required to provide consent before being given access to the screening survey (for survey data only). The SLUMBRx study will also require a consenting process. In this instance, informed consent will be obtained before initiating the laboratory-based study. In phase 1,

participants will be given a copy of the consent form to read in private and the opportunity to ask questions. They will be informed that declining to participate will in no way interfere with their relationship with the University of Alabama and that participation is voluntary, and they may withdraw at any point. The principal investigator (PI) will take every precaution to ensure that prospective participants understand what is being asked of them before signing the consent form. In addition to the screening survey, no data will be collected without obtaining informed, signed, written consent.

Data Storage, Confidentiality, and Privacy

Every effort will be made to ensure participant privacy. Data safety and monitoring will be evaluated by a data and safety monitoring board. Whenever feasible, identifiers are removed from the study-related information. All blood samples will be identified by a barcode generated by a computer in place of identifiable information. Data obtained for the proposed study will be used only for this research project. A review of informed consent documents for phases 1 and 2 of the SLUMBRx study will occur face-to-face with participants behind closed doors in a private interview room located within the Nutrition and Metabolism Research Lab. Lab-based data will be collected in patient rooms (behind closed doors with no windows in the room) located within the Nutrition and Metabolism Research Lab. All paper records will be kept in locked filing cabinets located within the PI's locked office (doubly locked) and will only be accessible to personnel involved in the study. All electronic records will be stored at the University of Alabama's password-protected HIPAA-compliant cloud service. Access to the cloud requires a password and confirmation from a second device using the Duo security platform. For example, when attempting to log on to the cloud, not only must the PI enter the correct password, but a confirmation of entry is sent to the PI's mobile device for confirmation of access. The password to the cloud will frequently change as an additional form of data protection. All interactions, including phone calls and emails, to and from participants will comply with HIPAA regulations.

Data Collection

Following a web-based screening survey of participants, qualified, consenting respondents will participate in a 2-phase SLUMBRx study. Phase 1 entails the collection of objective measures of adiposity and cardiometabolic outcomes. Phase 2 involves collecting subjective and objective sleep data using sleep diaries, actigraphy, and home sleep testing for sleep apnea. During phase 2, participants will also complete a battery of validated questionnaires and scales assessing socioecological factors associated with sleep, adiposity, and cardiometabolic outcomes.

Phase 1: Laboratory-Based Study

This component of the SLUMBRx study will allow for objective measures under controlled conditions typical of lab-based studies. Participants will be escorted to the Nutrition and Metabolism Research Lab, where they will review the study protocol and sign an informed consent form. Next, participants will undergo a battery of tests related to the measurement of adiposity and cardiometabolic indices outlined below.

Air-Displacement Plethysmography

The adult air-displacement plethysmography system, commercially produced under the trade name BOD POD (COSMED), has been validated [64,65] in adult populations and is considered robust for the measurement of human body composition [66,67]. Air-displacement plethysmography is a whole-body densitometric technique based on the displacement of air rather than water; it evaluates human body volume, body density, and body composition by measuring air displacement and the subsequent determination of body volume through the application of Boyle law. The air-displacement plethysmography unit consists of a dual-chamber plethysmograph, an electronic scale, and a computer. This equipment has a single structure containing 2 chambers separated by a device that produces pressure fluctuations and volume changes, permitting body volume assessment; this is followed by two to three 50-second measurements with the subject in the BOD POD using estimated thoracic lung volume to determine the fat mass, fat-free mass, and percentage body fat (%BF).

Anthropometrics

All measurements will adhere to standardized protocols, and anthropometric measures will all be performed by the same trained clinician. BMI will be calculated as body weight (in kilograms) without shoes and with light clothing, divided by height (in meters) squared—expressed as kg/m^2 . Body weight will be measured to 0.05 kg using the BOD POD electronic scale. Height will be measured to the nearest 1 mm using a stadiometer (Seca). For both height and weight, 2 measurements will be obtained and averaged; a third measurement will be obtained if the first two are more than 0.5 cm/0.1 kg apart and then averaged. Skinfold thicknesses will be measured to the nearest 0.1 mm with a skinfold caliper at the following sites using the same averaging protocol: (1) triceps, halfway between the acromion process and the olecranon process; (2) biceps, at the same level as the triceps skinfold, directly above the center of the cubital fossa; (3) subscapular, 20 mm below the tip of the scapula, at an angle of 45° to the lateral side of the body; and (4) suprailiac, 20 mm above the iliac crest and 20 mm toward the medial line. Circumferences will be measured with a nonelastic tape within 1 mm as follows: (1) waist circumference will be measured at the end of a gentle expiration midway between the lowest rib and iliac crest and (2) hips will be measured at the greater trochanter. In addition to standard circumference data, neck circumference will be measured because of its correlation with cardiometabolic risk [68] and sleep apnea in short sleepers [69]. Therefore, (3) neck circumference will be measured in the midway of the neck between the midcervical spine and midanterior neck. All skinfold and circumference measures will be taken with the participants standing upright, with the face directed toward the clinician, and shoulders relaxed.

Pulse Wave Velocity and Pulse Wave Analysis

Arterial stiffness will be assessed by radial artery applanation tonometry recording (Mobil-O-Graph [70]). Pulse wave analysis is a noninvasive, valid, reliable, and inexpensive technique that offers significant clinical and epidemiological potential. Briefly, pressure is applied to the radial artery by a probe placed on the

wrist. The radial wave created by the signal is used to generate an aortic pulse pressure waveform, which is used to derive an augmentation index (AI_x). AI_x is an indication of arterial stiffness, with a higher AI_x signifying greater arterial stiffness [39,40].

Blood Pressure

Hypertension has been proposed as an intermediate step in the causal pathway between decreased sleep duration and cardiovascular disease [57]. During the same visit, 2 systolic and diastolic blood pressure readings will be recorded (Mobil-O-Graph [71]) with a 5-minute interval and averaged for analysis. A third measurement will be obtained if the difference between the first two is >5 mm Hg [72]. Both blood pressure and pulse wave velocity or pulse wave analysis will be measured in a seated position after a 10-minute rest period in a quiet room.

Cardiometabolic Biomarkers

Sleep duration is hypothesized to influence cardiometabolic biomarkers [73]. Hyperlipidemia is an established risk factor for cardiovascular disease [74] and may be linked to short sleep [41]. Blood samples will be collected by a trained phlebotomist in the Nutrition and Metabolism Research Lab for measures of cholesterol (lipid panel with low-density lipoprotein:high-density lipoprotein ratio) and glucose [52]. Samples will be taken in a sitting position, centrifuged immediately, and transferred under cold chain conditions to a central laboratory for analysis.

Phase 2: Prospective Assessment

This component of the SLUMBRx study will allow for the sampling of adiposity, sleep, and cardiometabolic outcomes in a manner consistent with naturalistic or ambulatory studies.

Home Sleep Testing

During their visit to the Nutrition and Metabolism Research Lab, participants will be provided with a home sleep recording device that will be used to screen for sleep apnea by recording airflow, respiratory effort, and oxygen saturation. Participants will be instructed on the device's use and will be given a prepaid envelope to return the device. All recordings will be scored by trained technicians at the Alabama Neurology and Sleep Medicine. Participants with an apnea-hypopnea index of ≥ 5 will be referred for treatment [75].

Actigraphy and Questionnaires

Participants will complete a battery of questionnaires through a web-based data portal. Questionnaires will include the Sleep Timing Questionnaire (STQ) for habitual sleep schedule [76], the Epworth Sleepiness Scale (ESS) for subjective sleepiness [77], and the Pittsburgh Sleep Quality Index (PSQI) [56] for sleep quality. Participants will also complete sleep diaries [44] and wear an accelerometer for 1 week to provide an objective assessment of sleep, following the guidelines by Ancoli-Israel et al [78,79]. These assessments will be used to corroborate the retrospective measures of sleep duration. In addition, previously validated questionnaires and scales representing salient levels of the **socioecological** model of sleep (societal, social, and individual) developed by Grandner et al [12,33] will be completed by participants. Examples of questionnaires include

societal level [80,81] (Barriers to Care Questionnaire [82]), social level [83,84] (Job Satisfaction Survey [84]), and individual level [85,86] (Healthy Literacy Questionnaire [87], Self-Efficacy for Sleep Scale [88], and demographics such as education, marital status, annual household income, etc).

Potential Problems and Alternatives

If web-based data collection presents a significant barrier, especially as it pertains to the recruitment of women and/or minorities, paper-and-pencil versions of the data collection materials will be provided to respondents. An alert system will be incorporated into the web-based data portal to assist with compliance, alerting study staff if a questionnaire or diary entry has been missed. In addition, participants will be provided a 24/7 contact number and directions that will be tested for readability. Budgetary allowances for 10 additional participants (6.25%) were allocated as safeguards against attrition. Records of respondents' baseline characteristics will determine whether differences between those that participate and those that do not participate will be retained. If differences are identified, statistical adjustments will be made to account for possible selection bias. If violations to model assumptions are detected, problematic data will be inspected. If possible, model modifications (eg, transformation) will be made, rather than dropping cases. The risks involved in this study are minimal. Protocols will be enacted to manage potential risks.

Data Analytic Strategy and Analysis

Data Collection and Management

Most of the self-report data will be collected via a web-based portal (Qualtrics LLC) dedicated to the proposed study. Data from other sources will be entered into the same system by trained research staff. When the data are fully aggregated, they will be downloaded, screened, and summarized. A final analysis database will be constructed with all summary variables deidentified according to standardized confidentiality procedures.

Data Analysis Plan

The primary study variables for the SLUMBRx study include (1) sleep hours, (2) systolic blood pressure, (3) diastolic blood pressure, (4) apnea-hypopnea index, (5) augmentation index, (6) total lipid levels, and (7) glucose. It is hypothesized that, relative to participants who are normal weight, those who are overweight and obese will have differences in the distribution of the primary study variables reflected either in mean changes and/or increased variance. The primary study hypotheses will be tested using analysis of variance (ANOVA). ANOVA models utilize all available outcome data in the estimation of group differences for individual outcomes. Due to the potential correlation among cardiometabolic variables, a multivariate ANOVA omnibus test will be calculated to control for familywise type I error rate and assess patterns between multiple dependent variables. Then, univariate ANOVA for each dependent variable will be conducted as follow-up tests. A series of secondary outcome variables will also be analyzed using ANOVA models to examine group differences for a constellation of variables (eg, sleep quality, %BF, stroke volume, neck circumference, mean arterial pressure, etc).

Specific aim 4 is exploratory in nature. Due to the sample sizes required to build robust multilevel models, formal hypothesis testing will not be conducted.

Treatment of Missing Data

A multiple imputation approach will be used in the event of missing data [89]. Under this procedure, we will use SAS PROC.MI to complete data sets and combine these using SAS PROC.MIANALYZE to produce final inferential results. Sensitivity analysis will be conducted by comparing results from only complete cases and data imputed [90]. Table 1 summarizes the hypotheses, methods of analysis, and statistical models used for the SLUMBRx study. If the multiple imputation computation system fails to work correctly, then nonparametric analysis methods will be applied.

Discussion

Principal Findings

Obesity and short sleep duration are highly prevalent, interconnected risk factors for cardiometabolic disease in adults; however, a comprehensive adiposity-sleep model has remained elusive because of the complexity of the relationship between these 2 health-related states. The SLUMBRx study can help to drive preventative public health interventions by (1) probing the validity of the adiposity-sleep hypothesis, (2) modeling upstream and downstream demographic and ecological factors of adiposity and sleep, and (3) determining whether adiposity and sleep influence cardiometabolic disease risk factors. The proposed research will form the background of new lines of epidemiological and experimental inquiry seeking to unpack the relationship between adiposity, sleep, and cardiometabolic disease. Furthermore, this study will provide data necessary to propose and design public health interventions for obesity and short sleep duration by identifying appropriate measures to be used as intervention endpoints.

Conceptual Innovations

SLUMBRx is conceptually innovative in at least five ways. First, this proposal explores the potential of adiposity indices as modifiable risk factors for short sleep. If participants who are overweight and obese demonstrate shorter sleep than those who are of normal weight, it will lend credence to the hypothesis proposed in specific aim 1 that adiposity independently and/or interactively contributes to short sleep. Second, few studies have used rigorous adiposity measurement when investigating sex-based differences between sleep and adiposity as delineated in specific aim 2. Studies that have been conducted frequently produce conflicting or null results, suggesting that additional research is needed to understand this phenomenon. Third, sleep, adiposity, and cardiometabolic data will be collected predominantly from participants in underserved, rural settings (Tuscaloosa county in Alabama), with an anticipated high prevalence of short sleep (<7 hours, estimated at 46.1%) and obesity (estimated at 41.4%) [91]. Data collection in rural settings will inform recruitment strategies for future studies. Fourth, sleep assessment will be conducted both retrospectively (with the STQ [76], ESS [77], and PSQI [56]) and prospectively (home sleep testing, sleep diaries, and actigraphy). Retrospective

assessment using the STQ represents one of the first uses of a validated instrument to assess sleep schedules for identifying short sleepers. Prospective assessment, which is rarely done, is also important because it allows for determining whether self-reports of short sleep are reliable over time. Fifth, the data collected as part of specific aim 4 is innovative as research investigating upstream and downstream **socioecological** drivers of sleep is limited [20,78].

Methodological Innovations

The SLUMBRx investigation is also methodologically innovative in several ways. First, this proposal has the potential to drive public health intervention research by probing the validity of the obesity-sleep hypothesis using objective sleep and adiposity metrics. Second, the influence of sleep duration and adiposity indices on cardiometabolic outcomes, as detailed in specific aim 3, is a novel extension of the epidemiological and experimental body of research. Third, this project will assess the feasibility of public health sleep-based research undertaken in underserved, rural communities. It is also expected that the implementation of the protocol will inform recruitment strategies for future grants built off this proposal. Fourth, the data collected from this study will assist in proposing and designing future

public health interventions by identifying clinical endpoints for sleep, adiposity, and cardiometabolic outcomes. Fifth, this study will use a web-based data portal to provide convenient access to study materials for participants. In addition, the data portal will employ time stamping (assuring prospective data are indeed prospective) and content validation of response options (eg, restricting out-of-range responses). The system also eliminates data entry and transcription errors that can occur when transcribing paper-and-pencil data into electronic spreadsheets.

Conclusions

Obesity and short sleep duration in adults comprise prominent public health concerns because of their high prevalence and association with a wide range of harmful sequelae, including premature mortality [92], cardiovascular disease [3], and diabetes [93]. In recent years, there has been increased interest in the potential link between obesity and short sleep [11,13,26,94-96]. The proposed SLUMBRx investigation will contribute to developing a comprehensive adiposity-sleep model while also laying the groundwork for a future research program that aspires to prevent and treat adiposity and sleep-associated cardiometabolic disease risk factors.

Conflicts of Interest

None to declare.

Multimedia Appendix 1

Funded grant peer-review documentation.

[PDF File (Adobe PDF File), 157 KB - [resprot_v10i3e27139_app1.pdf](#)]

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Abbreviations

- %BF:** and percentage body fat
- AIx:** augmentation index
- ANOVA:** analysis of variance
- ESS:** Epworth Sleepiness Scale
- HIPAA:** Health Insurance Portability and Accountability Act
- NHANES:** National Health and Nutrition Examination Survey
- PI:** principal investigator
- PSQI:** Pittsburgh Sleep Quality Index
- SLUMBRx:** Short Sleep Undermines Cardiometabolic Health
- STQ:** Sleep Timing Questionnaire

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Protocol

Transition of Renal Patients Using AlloSure Into Community Kidney Care (TRACK): Protocol for Long-Term Allograft Surveillance in Renal Transplant Recipients

Bethany L Dale¹, PhD; Subhasish Bose^{2,3}, MD; Sheng Kuo⁴, MD; Alana Burns¹, MS; Pierre Daou¹, MD, MPH; Jenna Short¹, MBiol; Jake Miles¹, MD

¹CareDx, Brisbane, CA, United States

²Lynchburg Nephrology Physicians, Charlottesville, VA, United States

³Division of Nephrology, Department of Medicine, University of Virginia Medical Center, Charlottesville, VA, United States

⁴Nephrology Associates PC, Queens, NY, United States

Corresponding Author:

Jake Miles, MD

CareDx

1 Tower Place

9th Floor

Brisbane, CA, 94080

United States

Phone: 1 9293635937

Email: [jmiles@caredx.com](mailto:jmiles@ caredx.com)

Abstract

Background: Patients with end-stage kidney disease require complex and expensive medical management. Kidney transplantation remains the treatment of choice for end-stage kidney disease and is considered superior to all other modalities of renal replacement therapy or dialysis. However, access to kidney transplant is limited by critical supply and demand, making it extremely important to ensure longevity of transplanted kidneys. This is prevented through lifelong immunosuppression, with caution not to overly suppress the immune system, resulting in toxicity and harm. Transition of care to community nephrologists after initial kidney transplantation and monitoring at a transplant center is an important process to ensure delivery of effective and patient-centric care closer to home. Once transplanted, laborious surveillance of the immune system and monitoring for potential rejection and injury are undertaken through an armamentarium of screening modalities. Posttransplant surveillance for kidney function and injury remains key to follow-up care. While kidney function, quantified by estimated glomerular filtration rate and serum creatinine, and kidney injury, measured by proteinuria and hematuria, are standard biomarkers used to monitor injury and rejection posttransplant, they have recently been demonstrated to be inferior in performance to that of AlloSure (CareDx Inc, Brisbane, CA) circulating donor-derived, cell-free DNA (dd-cfDNA).

Objective: The outcomes and methods of monitoring renal transplant recipients posttransplant have remained stagnant over the past 15 years. The aim of this study is to consider intensive surveillance using AlloSure dd-cfDNA in an actively managed protocol, assessing whether it increases long-term allograft survival in kidney transplant recipients compared with current standard clinical care in community nephrology.

Methods: The study protocol will acquire data from a phase IV observational trial to assess a cohort of renal transplant patients managed using AlloSure dd-cfDNA and patient care managers versus 1000 propensity-matched historic controls using United Network for Organ Sharing U.S. Scientific Registry of Transplant Recipients data. Data will be managed in a centralized electronic data server. The primary outcome will be superior allograft survival, as a composite of return to dialysis, retransplant, death due to allograft failure, and death with a functional graft (infection, malignancy, and cardiovascular death). The secondary endpoints will assess improved kidney function through decline in estimated glomerular filtration rate and immune activity through development of donor-specific antibodies.

Results: The total sample is anticipated to be 3500 (2500 patients managed with AlloSure dd-cfDNA and 1000 propensity-matched controls). Active enrollment began in November 2020.

Conclusions: Based on a significant literature base, we believe implementing the surveillance of dd-cfDNA in the kidney transplant population will have a positive impact on graft survival. Through early identification of rejection and facilitating timely intervention, prolongation of allograft survival versus those not managed by dd-cfDNA surveillance protocol should be superior.

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KEYWORDS

donor-derived cell free DNA (dd-cfDNA); molecular inflammation; molecular injury; acute rejection; allograft injury; allograft surveillance; renal transplant; renal; transplant; injury; graft rejection; kidney; kidney disease; transplantation

Introduction

The recent presidential executive order to advance American kidney health has directed the U.S. Department of Health and Human Services to increase the number of patients with new end-stage kidney disease (ESKD) to either receive dialysis at home or receive a transplant, with the aim to double the number of kidneys transplanted by 2030 [1].

With over 700,000 patients living with ESKD in the United States, ensuring allograft longevity post-kidney transplant is critical [2]. As compared with dialysis, kidney transplantation is known to provide superior quality of life, patient survival, and cost-effectiveness [3-6].

Minimally invasive biomarkers to detect allograft injury and rejection have become increasingly important as clinicians strive to develop new strategies for personalization of medicine and prolonging allograft survival. Since its discovery in 1948, cell-free DNA has had a significant impact on molecular diagnostics and is now utilized frequently in prenatal genetic screening, preclinical neoplasia detection, and more recently, solid organ transplantation [7]. In recent years, donor-derived, cell-free DNA (dd-cfDNA) has shown clinical validity as a leading biomarker of allograft inflammation and injury [8-11].

In the Circulating Donor-Derived Cell-Free DNA in blood for diagnosing Acute Rejections in Kidney Transplant Recipients (DART) study, Bloom et al [8] assessed 102 paired renal allograft biopsies with dd-cfDNA. The median levels of dd-cfDNA in patients with a histological diagnosis of active rejection were significantly elevated compared to those without active rejection (1.6% versus 0.3%, $P < .01$). The receiver-operating characteristic area under the curve was reported at 0.74, which significantly outperformed serum creatinine at 0.54 in detecting active rejection. The performance characteristics of this assay were improved when discriminating antibody-mediated rejection (ABMR) from no ABMR, with an area under the curve of 0.87 [8]. Huang et al [10] validated these findings in a single-center study assessing 63 highly sensitized renal transplant patients with paired allograft biopsies and AlloSure dd-cfDNA.

More recently, in the Resolution by AlloSure Differentiates Ambiguous Rejection (RADAR) study, Stites et al found that AlloSure dd-cfDNA $>0.5\%$ can aid in the risk stratification of patients with T-cell mediated rejection grade 1A or borderline rejection with respect to poor clinical outcomes identified as estimated glomerular filtration rate (eGFR) decline, de novo

donor-specific antibody (DSA) formation, and recurrent rejection episodes [11].

AlloSure dd-cfDNA has also shown associations with de novo DSA formation and ABMR previous to RADAR. Jordan et al [12] identified 90 dd-cfDNA samples paired with DSAs and clinically indicated biopsies and demonstrated the combination of dd-cfDNA and DSA testing improved the diagnostic yield of noninvasive diagnosis of ABMR to 89% positive predictive value.

Understanding the severity of opportunistic infections in immune-suppressed patients resulting in kidney injury is another area of utility. dd-cfDNA has been demonstrated to aid in differentiation of BK viremia and BK nephropathy, as well as help in cases with high viral copy number and confounding biopsy results [13,14].

Further, it is estimated that 60% of late rejections and 30% of early rejections can be attributed to posttransplant nonadherence to immunosuppressants. A meta-analysis and systemic review demonstrated patients who receive adherence intervention have significantly higher compliance (odds ratio=2.366) [15]. Transplant centers currently utilizing patient care managers (PCMs) also have improvements in patient adherence, upwards of 30% (unpublished data). These findings, in conjunction with other supporting evidence, demonstrate that the analysis of dd-cfDNA and PCM support are helpful in the assessment of transplant patients and provide additional information of allograft status.

In addition to allograft rejection, the clinical significance of other morbidity-affecting outcomes remains significant. Malignancy, infection, cardiovascular complications, and bone complications are an inevitable consequence of a lifetime of immunosuppression, adding a significant burden on patients and the health care system. Management of these patients is complex and often multidisciplinary, where AlloSure can provide additional, previously lacking, information about the allograft. This was recently demonstrated in a case report by Lipson et al [16] in the management of a renal transplant recipient (RTR) on checkpoint inhibitors to treat malignancy.

Death with a functioning graft (DWFG) accounts for 47% of all transplant losses after 10 years. Additionally, registry data and retrospective analyses of long-term outcomes from randomized trials have highlighted cardiovascular disease, followed by malignancy as the top causes of morbidity and DWFG. However, while death from cardiovascular disease in

RTRs appears to be declining, mortality from malignancy is increasing [17].

The increasing number of transplants worldwide is further resulting in a growing cohort of posttransplant recipients (179,361 RTRs in the United States in 2010); due to the limited number of transplant nephrologists, these patients are increasingly likely to encounter practitioners in other specialties. Thus, understanding the value of AlloSure dd-cfDNA in the context of long-term management is an area of key importance. The aim of this study is to assess the value of AlloSure dd-cfDNA and an actively managed protocol in the context of chronic complications and determine how it may influence long-term outcomes relevant to generalists.

As the number of kidney transplants performed continues to increase in the United States, so does the cohort of long-term RTRs, which was estimated at over 220,000 in 2017 [18]. With limited transplant nephrologists and hospital outpatient resources, many of these patients will be managed under a shared care model between community physicians and transplant centers. The Transition of Renal patients using AlloSure into Community Kidney care (TRACK) study aims to assess the utility of AlloSure dd-cfDNA surveillance and supplemental patient care management for RTRs in prolonging allograft survival and improving long-term clinical outcomes including graft function and immunological status.

Methods

Study Design

This is a phase IV, prospective, multicenter, observational, cohort study designed to evaluate the effectiveness of AlloSure dd-cfDNA (CareDx Inc, Brisbane, CA) surveillance and patient care management in kidney transplant patients in prolonging allograft survival, allograft function, and immunological status. All prospective data will be collected from patient electronic medical records. Propensity-matched control data will be

sourced from United Network for Organ Sharing U.S. Scientific Registry of Transplant Recipients databases. The study duration will be event driven, with each patient's enrollment lasting 5 years.

Outcomes and Measures

The primary endpoint of this study will be superior graft survival measured as the time to allograft loss, defined as the composite of return to dialysis, retransplant, death due to allograft failure, and DWFG (infection, malignancy, and cardiovascular death).

Secondary endpoints include assessment of allograft function and immunological status. Allograft function will be measured as the relative change in eGFR from baseline between the 2 study groups: dd-cfDNA surveillance compared to controls. Immunological status will be defined by detection of de novo DSA formation in patients monitored using dd-cfDNA compared to the matched controls.

All clinical events and investigation results will be captured through the patient electronic medical record or via AlloCare, an optional smartphone-based application that provides a patient-driven platform to manage medications, access results, monitor wellness activities, and streamline communication with their care team. Patients will also be offered mobile phlebotomy when they are unable to visit a local laboratory. The mobile blood draw will be coordinated by CareDx, which will draw all regular tests, urine samples, as well as the AlloSure. Support for testing adherence will be provided by PCMs (CareDx Inc, Brisbane, CA) to assist with scheduling both in-center and mobile draws and provide laboratory visit reminders.

Testing Schedule

Patients will have quarterly AlloSure dd-cfDNA testing (every 3 months) as part of their posttransplant surveillance for a period of 5 years. DSA, eGFR, routine transplant bloods, and clinical events will be captured using the standard of care regime as per institutional guidelines (Figure 1).

Figure 1. Schedule of testing events. dd-cfDNA: donor-derived cell-free DNA; DSA: donor-specific antibody; eGFR: estimated glomerular filtration rate; EMR: electronic medical record.

Months post enrollment	0	1	2	3	4	5	6	7	8	9	10	11	12
dd-cfDNA	x			x			x			x			x
DSA*	x			x			x			x			x
eGFR/bloods*	x	x	x	x	x	x	x	x	x	x	x	x	x
App/EMR Clinical event*	x	x	x	x	x	x	x	x	x	x	x	x	x
Months post enrollment		13	14	15	16	17	18	19	20	21	22	23	24
dd-cfDNA				x			x			x			x
DSA*				x			x			x			x
eGFR/bloods*		x	x	x	x	x	x	x	x	x	x	x	x
App/EMR clinical event*		x	x	x	x	x	x	x	x	x	x	x	x
Months post enrollment		25	26	27	28	29	30	31	32	33	34	35	36
dd-cfDNA				x			x			x			x
DSA*				x			x			x			x
eGFR/bloods*		x	x	x	x	x	x	x	x	x	x	x	x
App/EMR clinical event*		x	x	x	x	x	x	x	x	x	x	x	x
Months post enrollment		37	38	39	40	41	42	43	44	45	46	47	48
dd-cfDNA				x			x			x			x
DSA*				x			x			x			x
eGFR/bloods*		x	x	x	x	x	x	x	x	x	x	x	x
App/EMR clinical event*		x	x	x	x	x	x	x	x	x	x	x	x
Months post enrollment		49	50	51	52	53	54	55	56	57	58	59	60
dd-cfDNA				x			x			x			x
DSA*				x			x			x			x
eGFR/bloods*		x	x	x	x	x	x	x	x	x	x	x	x
App/EMR clinical event*		x	x	x	x	x	x	x	x	x	x	x	x

*Data captured as standard of care.

In the event of an allograft biopsy (surveillance or for-cause), dd-cfDNA testing is suggested to be drawn prior to the biopsy. For patients with a histological diagnosis of allograft rejection and who are hospitalized, dd-cfDNA are suggested to be measured on alternative days while inpatient and then paired with routine blood tests in the immediate 12 weeks following discharge with the goal to assess the response to treatment.

Patient Care Managers

PCMs will work directly with participating centers to assist with study protocol adherence and support the integration of

the AlloCare phone application. PCMs will coordinate mobile home phlebotomy draws, provide patient education, maintain AlloSure standing order requests in line with the study testing schedule, and provide logistic support to both centers and patients alike.

Rationale for Testing Schedule

The rationale of the quarterly assessment of dd-cfDNA in the context of renal transplantation is based on key milestones in the posttransplant care of patients and aligns with the routine testing for baseline transplant bloods, urinalysis, and DSA

monitoring. Commencing periodic dd-cfDNA surveillance at the 6-month time point posttransplant also complements the transition of care back to community nephrologists for many patients.

Antibody-mediated rejection is widely recognized as the leading cause of transplant failure and accounts for approximately two-thirds of renal allograft losses. Clinical studies over the last 10 years have established that antibodies generated de novo posttransplantation against DSAs are strongly associated and may be an important cause of allograft loss. Detection of a significant level of de novo DSAs should prompt verification of medication compliance and identification of potential sensitization events to minimize the risk of future rejection episodes [19]. Additionally, new data suggest that the elevation of dd-cfDNA precedes de novo DSA formation and correlates with increasing mean fluorescence intensity [12,20]. With the increasing risk of ABMR, assessing dd-cfDNA at these intervals allows practitioners to identify early molecular allograft injury.

Textbox 1. Study selection criteria.

Inclusion Criteria
<ul style="list-style-type: none"> • First draw for purposes of this study ≥ 6 months and ≤ 18 months from date of transplant • Kidney transplant recipient (retransplant and dual kidney permitted) • Patient's health care provider adopts and intends to apply the AlloSure Routine Testing Schedule (quarterly draws) • Participant is willing and able to give informed consent for participation in the trial • Male or female, aged 12 years or older • In the investigator's opinion, patient is able and willing to comply with all trial requirements
Exclusion Criteria
<ul style="list-style-type: none"> • Participant who is pregnant, lactating, or planning pregnancy during the trial • Significant hepatic impairment (determined by the principal investigator) • Participant with life expectancy of < 6 months or inappropriate for diagnostic monitoring through regular blood sampling • < 6 months and > 18 months posttransplant • Any other significant disease or disorder which, in the opinion of the investigator, may either put the participants at risk because of participation in the trial or may influence the result of the trial or the participant's ability to participate in the trial • Participants who have participated in another research trial involving an investigational product in the past 12 weeks • Recipients of multiorgan transplant (eg, kidney-pancreas) • Recipients of a transplant from a monozygotic (identical) twin • Recipients of nonautologous bone marrow transplant • Patients with a history of poor compliance or needle phobia

A 2-sided log-rank test with an overall sample size of 3500 kidney transplant patients (of which 2500 will be periodically assessed with AlloSure and 1000 are matched controls receiving standard of care) achieves 87% power at a 5% significance level to detect an allograft survival difference of 5% (ie, 75%, AlloSure assessed; 70%, standard of care) during the 5-year surveillance period. This corresponds to a hazard ratio of 0.807, which is a 19.3% reduction in the risk of allograft loss in the AlloSure-assessed patients in comparison to standard of care. There is no consideration of patients lost to follow-up due to the United Network for Organ Sharing U.S. Scientific Registry of Transplant Recipients database, which tracks transplanted

Preliminary data are suggestive that elevated dd-cfDNA within the first year posttransplant is associated with significant eGFR decline of 25% in the subsequent year [21]. Quarterly surveillance allows identification of patients that may require increased surveillance and intervention while allowing longitudinal assessment to discern if these trends are appreciated during long-term follow-up.

Participants

All patients who underwent a kidney transplant within ≥ 6 months and ≤ 18 months will be screened to identify patients who are eligible for the study based on inclusion and exclusion criteria. Patients who are eligible to enter the study will be approached for consent during their routine posttransplant clinic visits and will be considered enrolled when they have signed the informed consent form. Selection criteria are shown in [Textbox 1](#).

organ survival for all organ transplant recipients; however, this analysis does account for an attrition rate of 65%.

A decline in GFR has been shown to be a valid surrogate for long-term outcome in renal transplantation. A 2-sided *t* test or its nonparametric analog will be used to assess differences in the distribution of 5-year change from baseline in eGFR between AlloSure and standard of care surveillance groups. These tests will have approximately 76% power at a 5% significance level to detect a 25% difference in eGFR decline over the 5-year surveillance period. This assumes, over the 5-year surveillance period, an average of 12 mL/min per 1.73 m² decline in eGFR

for standard of care and an average 9 mL/min per 1.73 m² decline in eGFR for AlloSure (both groups having similar standard deviations of 30 mL/min per 1.73 m²).

Assuming the proportion of control subjects with formation of de novo DSA antibodies during the 5-year surveillance period is 40%, a 2-sided Z-test with continuity correction and pooled variance with the aforementioned sample size of 3500 achieves 78% power at a 5% significance level to detect a de novo DSA formation difference of 5% (ie, 35%, AlloSure assessed; 40%, standard of care) during the 5-year study surveillance period.

Statistical Analysis

Data will be assessed for normalization and are likely to be nonparametric. Appropriate statistical tests will be applied with the final analysis occurring at the end of the study. Statistical assessments resulting in a *P* value <.05 will be deemed significant. All participants who have at least one AlloSure assessment during the surveillance period will be included in the analysis.

Results

This study received Western Internal Review Board approval in September 2020. A total of 20 community nephrology practices are expected to participate in this study. Active enrollment began in November 2020. Study insights and conclusions are expected to be presented intermittently throughout the study at international conferences and manuscripts submitted to peer-reviewed academic journals.

Discussion

Patients undergoing kidney transplantation (either de novo or retransplant) are routinely surveyed with interval blood tests as part of standard postoperative care through outpatient consultation. These tests include serum creatinine, immunosuppressive drug levels, complete blood count, urinalysis, and DSA testing at various intervals. The ability to screen patients to accurately risk-stratify those likely to develop an adverse event using dd-cfDNA is likely to be advantageous, with the potential to improve graft survival and outcomes for transplant patients.

As we evolve our understanding of dd-cfDNA as a leading indicator of poorer outcomes, monitoring longitudinal trends of dd-cfDNA may help risk-stratify the patient population prior to development of graft dysfunction. Elevations in dd-cfDNA are a complementary indicator of graft health and immunological quiescence, helping to further augment and improve our current assessment capabilities and conceivably facilitate earlier intervention. Additionally, the levels of dd-cfDNA can track real-time response to treatment due to a short half-life, be used as an adjuvant marker with histological findings to predict eGFR

decline, stratify patients that are likely to develop de novo DSA, and allow optimization of immunosuppression safely over time [11,22,23].

PCM support is designed to facilitate protocol adherence and assist with scheduling mobile blood draws for surveillance testing. Analogous to the function of transplant coordinators, PCMs can support patients with education, appointment scheduling, logistical solutions, and coordination of care to drive adherence and improvements in delivery of posttransplant care. Maintaining protocol adherence aims to enhance allograft surveillance and identify clinical events early, allowing for tailored interventions to improve patient outcomes.

By providing a surveillance tool like AlloSure and patient care management to community nephrologists via TRACK, we can allow a more comprehensive assessment of the patient and allograft beyond the traditional measures such as eGFR, creatinine, and DSA values. With TRACK, when a patient has transitioned to a community center, they will continue to have access to dd-cfDNA testing to monitor allograft status. Longitudinal surveillance of dd-cfDNA will provide an understanding of patient-specific baselines, which serve as a reference point to identify actionable changes in dd-cfDNA that may indicate significant clinical events requiring further investigations and intervention.

This study will also be conducted over a duration of 5 years postenrollment. While the 1-year survival of many kidney transplants is quite good, those further from transplant have worsening survival. This extended timeline is essential to understanding allograft survival, as there is a rapid decline in allograft failure after 3 years posttransplant. Therefore, the longer-term survival of those managed with AlloSure dd-cfDNA and close patient care management will be the primary aim of this study.

While a vast majority of clinical practice adheres to a standard schedule, transplantation is unique in that the timeframe and the testing modality schedule are specific to each transplant center. This heterogeneity is further divided once a patient transfers from the transplant center to the community practice. With this patient population, we acknowledge not every patient will be monitored for DSA or standard labs at the same intervals. The data capture system will be designed to accommodate a quarterly window for the labs that are available to correlate with the AlloSure dd-cfDNA draws.

The TRACK study will assess the validity of dd-cfDNA surveillance and patient care management in kidney transplant patients, aiming to demonstrate superior allograft survival, graft function, and immunological status. This will provide important insights into risk factors for poor clinical outcomes, detect molecular allograft injury and rejection, and identify opportunities for early intervention.

Conflicts of Interest

This study was supported by CareDx Inc, Brisbane, CA. BD, AB, PD, JM, and JS are paid full-time employees of CareDx, Inc. SB is the Principal Investigator of the TRACK study sponsored by CardDx.

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Abbreviations

ABMR: antibody mediated rejection

DART: Circulating Donor-Derived Cell-Free DNA in blood for diagnosing Acute Rejections in Kidney Transplant Recipients

dd-cfDNA: donor-derived cell-free DNA

DSA: donor-specific antibody

DWFG: death with functioning graft

eGFR: estimated glomerular filtration rate

ESKD: end-stage kidney disease

PCM: patient care manager

RADAR: Resolution by AlloSure Differentiates Ambiguous Rejection

RTR: renal transplant recipient

TRACK: Transition of Renal patients using AlloSure into Community Kidney care

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Protocol

Implementation of the Living Well During Pregnancy Telecoaching Program for Women at High Risk of Excessive Gestational Weight Gain: Protocol for an Effectiveness-Implementation Hybrid Study

Susan de Jersey^{1,2}, BHLthSci, BAppSci, MPH, PhD; Nina Meloncelli^{1,3}, BNutrDiet(Hons), PhD; Taylor Guthrie², BHsc(Hons); Hilary Powlesland², BBus, BNutrDiet; Leonie Callaway^{4,5}, MBBS, PhD; Angela T Chang⁶, BPhy(Hons), PhD; Shelley Wilkinson⁷, BSc, GDND, PhD; Tracy Comans^{6,8}, BPhy, BEcon(Hons), PhD; Elizabeth Eakin⁹, BA, PhD

¹Centre for Clinical Research and Perinatal Research Centre, Faculty of Medicine, The University of Queensland, Brisbane, Australia

²Department of Nutrition and Dietetics, Royal Brisbane and Women's Hospital, Metro North Hospital and Health Service, Brisbane, Australia

³Allied Health, Metro North Hospital and Health Service, Brisbane, Australia

⁴Department of Obstetric Medicine, Royal Brisbane and Women's Hospital, Brisbane, Australia

⁵Faculty of Medicine, University of Queensland, Brisbane, Australia

⁶Centre for Allied Health Research, Royal Brisbane and Women's Hospital, Metro North Hospital and Health Service, Brisbane, Australia

⁷School of Human Movements and Nutrition Sciences, The University of Queensland, Brisbane, Australia

⁸Centre for Health Services Research, Faculty of Medicine, The University of Queensland, Brisbane, Australia

⁹School of Public Health, Faculty of Medicine, The University of Queensland, Brisbane, Australia

Corresponding Author:

Susan de Jersey, BHLthSci, BAppSci, MPH, PhD

Centre for Clinical Research and Perinatal Research Centre

Faculty of Medicine

The University of Queensland

Building 71/918

RBWH Herston

Brisbane

Australia

Phone: 61 424949217

Email: susan.dejersey@health.qld.gov.au

Abstract

Background: Despite comprehensive guidelines for healthy gestational weight gain (GWG) and evidence for the efficacy of dietary counseling coupled with weight monitoring on reducing excessive GWG, reporting on the effectiveness of interventions translated into routine antenatal care is limited.

Objective: This study aims to implement and evaluate the Living Well during Pregnancy (LWdP) program in a large Australian antenatal care setting. Specifically, the LWdP program will be incorporated into usual care and delivered to a population of pregnant women at risk of excessive GWG through a dietitian-delivered telephone coaching service.

Methods: Metrics from the RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) framework will guide the evaluation in this hybrid effectiveness-implementation study. All women aged ≥ 16 years without pre-existing diabetes with a prepregnancy BMI > 25 kg/m² and gaining weight above recommendations at < 20 weeks' gestation who are referred for dietetic care during the 12-month study period will be eligible for participation. The setting is a metropolitan hospital at which approximately 6% of the national births in Australia take place each year. Eligible participants will receive up to 10 telecoaching calls during their pregnancy. Primary outcomes will be service level indicators of reach, adoption, and implementation that will be compared with a retrospective control group, and secondary effectiveness outcomes will be participant-reported anthropometric and behavioral outcomes; all outcomes will be assessed pre- and postprogram completion. Additional secondary outcomes relate to the costs associated with program implementation and pregnancy outcomes gathered through routine clinical service data.

Results: Data collection of all variables was completed in December 2020, with results expected to be published by the end of 2021.

Conclusions: This study will evaluate the implementation of an evidence-based intervention into routine health service delivery and will provide the practice-based evidence needed to inform decisions about its incorporation into routine antenatal care.

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KEYWORDS

implementation study; pregnancy; weight; nutrition; lifestyle intervention; physical activity

Introduction

Background

Excessive gestational weight gain (GWG) is a problem within the Australian obstetric population, occurring in 40% to 60% of pregnancies, particularly in the 50% of women already above a healthy weight prior to pregnancy [1]. This weight gain is associated with costly adverse medical and obstetric complications and contributes to the development of obesity in mothers and their offspring [2].

In Australia, comprehensive guidelines for healthy GWG from the Institute of Medicine (IOM [2]) have been widely promoted. Dietary counseling and weight monitoring have been shown to be effective in reducing GWG in research contexts and in routine antenatal care [3-5]. However, women already overweight before pregnancy are at greatest risk of excessive GWG [6], experience greater barriers to achieving a healthy weight gain, have lower confidence to achieve health goals [7], and have a need for more intensive support [8].

In addition, poor uptake of the typical clinical (face-to-face) model of dietetic counseling is seen in both research trials [9,10] and routine antenatal care services [11,12]. A face-to-face model of care to reduce GWG in overweight and obese pregnant women at our metropolitan tertiary hospital was poorly attended, and less than 10% of eligible women were referred [13,14]. Barriers to referral and engagement are likely multifactorial, with many women citing work commitments, timing, location [15], transport, and travel [16] as reasons for nonattendance.

Telephone counseling has been demonstrated as an effective and cost-effective solution for delivering positive weight management outcomes in a wide range of adult populations [17-19]. Individualized advice can be provided without requiring additional hospital visits and aligns with the preferences of women identified in formative work [20]. While various telephone-based interventions (either telephone counseling or text messages) have been trialed in the at-risk pregnant population, results have been varied, with limited reporting on the feasibility and cost-effectiveness of the approach within routine antenatal care settings [19,21]. This study aims to implement and evaluate the Living Well during Pregnancy (LWdP) program targeting pregnant women at risk of excessive GWG and delivered via telephone within the dietetic service in a large Australian tertiary setting. This program will be evaluated using metrics from the RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) framework, which includes effectiveness and implementation outcomes [22].

Methods

Study Design

The LWdP program will use a type 2 effectiveness-implementation hybrid design [23] to compare prospectively gathered data on participants enrolled in the LWdP program with a retrospective comparison group who was referred to the dietitian for pregnancy weight management. The setting is a tertiary metropolitan hospital that delivers approximately 4500 babies per year and offers 8 different models of antenatal care for both high- and low-risk pregnancies, including general practitioner shared care. These models of antenatal care will be consistent across the retrospective (preimplementation) and prospective (postimplementation) study periods. The retrospective control group will comprise pregnant women referred for dietetic care in the 12 months prior to the study period who meet the inclusion criteria. The prospective group will be consenting participants in the LWdP program referred for dietetic care during the 12-month study period. The RE-AIM evaluation framework will be used to understand the following about the LWdP program: reach and adoption (the number and representativeness of service referrers and participants), implementation (number of referrals, consent rates, fidelity of delivery, program completion rates, and costs of delivery), and effectiveness (maternal and neonatal outcomes) [22]. Evaluating the maintenance domain will not be possible within the time frame of the study. Ethics approval was granted from the Royal Brisbane and Women's Hospital Human Research Ethics Committee (HREC/17/QRBW/159).

Participants and Referral Pathways

All women aged ≥ 16 years without pre-existing diabetes with a prepregnancy BMI >25 kg/m² who are referred for dietetic weight management care during the study period will be eligible for participation. For the purpose of this evaluation, participants must be able to speak and read English sufficiently to allow program participation. Those women who do not meet these criteria will be provided with appropriate face-to-face dietetic care and not participate in this evaluation. Women will be referred into the program by their treating health care provider if they meet these criteria. Alternatively, women meeting these criteria will be able to self-refer into the program through a dedicated program website. Women who are engaged in the program who develop gestational diabetes will be provided the option to remain in the program or withdraw to the hospital's gestational diabetes model of care.

Engagement Strategy

Staff will be engaged in the planning phase of LWdP program implementation to identify preferred referral processes for each of the hospital's 8 different antenatal models of care. This will inform the introduction of an outpatient dietetic referral form for the LWdP program alongside other dietetic services at the facility and the inclusion of the LWdP program referral in paperwork completed during women's initial booking-in appointment. A program website will be developed to facilitate an online referral pathway, allowing both self-referral and referral by external antenatal health care providers located in the community of women under their care. A consumer engagement survey will be undertaken to inform the flexible program delivery hours, education needs, and topics of interest. Staff from each antenatal model of care will be provided with regular in-services, and the hospital's media and communications team will be engaged to help build publicity for the program by featuring consumer stories in local newsletters, social media accounts, and local general practitioner communications.

Screening and Consent

A waiver of participant consent was received as part of the ethics application to retrospectively access routinely collected clinical and administrative data from eligible women in the preimplementation group. For the postimplementation group, all women booked for an initial appointment in the LWdP program will be provided with an electronic link to the participant information sheet and electronic consent form with their participant workbook.

At the commencement of the program, the dietitian counsellor will discuss the evaluation process and answer any questions the participant may have. Program participants who consent to the evaluation will be requested to complete the consent form online in addition to having verbal consent recorded in their health record.

At the completion of the program, participants who verbally agreed to be involved in the evaluation but did not complete the consent form will be reminded to complete this online and a replacement link will be sent if required. Verbal consent will be documented on this second occasion. If no written consent form is received by the time of data analysis but two occasions of verbal consent are documented in the participant's health record, consent to participate in the evaluation will be considered granted.

LWdP Program

The LWdP program is aimed at supporting women at high risk of excessive weight gain during pregnancy to achieve GWG

within recommendations [2] through the promotion of healthy eating and physical activity. Consistent with Australian dietary guideline recommendations for pregnancy and chronic disease prevention [24], participants will be encouraged to choose whole-grain cereal products, increase fruit and vegetable intake (5 servings of vegetables and 2 servings of fruits per day), choose foods with unsaturated fat, and limit discretionary food choices. They will also be encouraged to focus on eating the right amount of food through portion control and intuitive eating and choosing the right types of foods (minimally processed, low energy density, and high nutrient density). Over the course of the intervention, participants with no contraindications will also be encouraged to gradually undertake pregnancy-appropriate planned physical activity (such as walking, swimming, yoga) to accumulate 150 minutes per week [25]. An additional focus will be on reducing sitting time to contribute to energy expenditure. The goal is for women to track within the target healthy GWG range recommended by the IOM guidelines [2] based on their prepregnancy BMI through changing eating and activity behaviors.

Women referred to the program will be eligible for up to 10 telephone coaching calls over the course of their pregnancy that will usually span a period of 6 months (1 call each week for 1 month, then 1 call every 2 weeks for the next month, then 1 call per month for the next 4 months) and will also receive a participant workbook (Textbox 1). The initial telephone call will be approximately 60 minutes in duration, with subsequent calls lasting approximately 30 minutes, with an emphasis on motivational interviewing [26] and tailored health behavior coaching [27]. The program has been adapted for pregnancy from the Healthy Living after Cancer program [28] and informed by previous formative work with women participating in the New Beginnings Healthy Mothers and Babies study at the same institution [1,20,29,30]. Specifically, the program will target behavioral constructs and consumer experiences gained from prior research with the study population [1,20,29,30]. The intervention is grounded in the social cognitive theory constructs of self-efficacy, social support, and outcome expectancies [31] and emphasizes developing skills using behavior change strategies—goal setting, self-monitoring, identifying potential barriers and problem solving, identifying social support, stimulus control, mindful eating, positive self-talk, and self-reward. The protocol for each call includes an assessment of progress, problem solving, advice/education, collaborative goal setting/goal progression, and development/revision of a behavior-specific action plan. The program topics have been mapped to the refined taxonomy of behavior change techniques [32], as shown in Multimedia Appendix 1.

Textbox 1. Living Well during Pregnancy participant workbook content.

Introduction to the Living Well during Pregnancy program

- Coach introduction, scheduling, and discussion of the importance of healthy weight gain in pregnancy

Section 1: Planning for success

- Participant aims
- SMART (Specific, Measurable, Achievable, Relevant, and Timed) goal setting and action plan
- Problem solving
- Tracking tools for eating behaviors, physical activity, weight gain, and meal planning

Section 2: What to eat and how much

- Benefits of healthy eating and recommendations in pregnancy
- Important nutrients (including supplementation)
- Portion guide
- Self-monitoring

Section 3: Fat, fiber, and food safety

- Increasing intake of fruits, vegetables, and whole grains
- Reducing saturated fat intake
- Food safety

Section 4: Keeping active

- Safe exercise during pregnancy
- Planning activity
- Pelvic floor exercises
- Reducing sitting time

Section 5: Healthy pregnancy weight gain and energy balance

- Energy density and food substitutions
- Strategies to slow rapid weight gain
- Healthy snacking

Section 6: Meal planning and preparation

- Creating healthy meals
- Grocery shopping planning
- Plating portion guide
- Strategies for healthy eating away from home

Section 7: Mindful eating

- Breaking the dieting cycle
- Hunger cues
- Mindful eating
- Overeating triggers
- Food and emotions

Section 8: Celebrating success and planning ahead

- Planning ahead
- Potential obstacles
- Celebrating success

- Getting support from others
- Healthy eating during breastfeeding

Accredited Practising Dietitians with experience in providing antenatal care services who have undergone additional training in motivational interviewing will be trained in the delivery of the program. A training manual detailing the program protocol including call transcripts will be provided to all dietitians delivering the program. This additional training includes program philosophy, person-centered care, work shadowing, and the delivery of each call with provision of feedback from the trainer and a checklist of training requirements prior to commencing program delivery. At the completion of each call, the dietitian coach will be required to complete a fidelity checklist to assess the degree to which the call aligned with the protocol.

The program is structured to offer flexibility in the scheduling of call times outside of usual business hours, with early morning and evening times available. Additionally, a caseload continuity of care model will be offered where each participant is allocated one dietitian coach for their pregnancy. Upon booking the first coaching session, each participant will be provided with a welcome letter with information about her coach to assist with establishing rapport.

Intervention Procedures

The participant workbook will be used to structure the order of intervention topics for each telecoaching session ([Textbox 1](#)). Participants will be encouraged to commence with a focus on healthy eating, as there is strong evidence to support dietary interventions for moderating pregnancy weight gain [33,34]. However, the intervention is tailored to meet individual participant's needs and motivations.

In the telephone-delivered program, the calls are structured into three phases ([Multimedia Appendix 2](#)), with weekly, biweekly, and then monthly phone calls. Frequent contact at the beginning of the program provides more intensive support for behavior change from the outset. Less frequent contact in the latter part of the program facilitates participants' autonomy and confidence in consolidating and maintaining lifestyle changes such that they will (optimally) become lifelong habits.

Usual Care

The retrospective group was provided with traditional, unstructured face-to-face dietetic care. Women were offered individual appointments with the dietitian in a dedicated clinic within the maternity outpatient department. An initial appointment was booked for 40 minutes, with review appointments allocated 20 minutes. There was no guarantee of the same dietitian at each review appointment, and review appointments were booked based on clinical judgment in negotiation with the woman. No specified educational content or strategies were provided.

Data Collection

Data will be collected by study-trained dietitian research assistants. Research Electronic Data Capture (REDCap), a secure online survey and data capture tool, will be used to record details of each telephone counselling session including progress, clinical information, and fidelity to the call procedures and topics. Routinely collected maternal and infant data will be accessed from medical records.

Primary and Secondary Outcomes

Outcomes are shown in [Table 1](#) along with corresponding RE-AIM indicators and assessment tools. Details of validated tools to be used are provided below. Primary outcomes will include referrals and referral sources, uptake among eligible patients, withdrawal rates and reasons (where available), completion rates, average number of calls per participant, average length of calls per participant, completion of pre-post program assessments, staff and participant satisfaction, and program delivery costs. Secondary outcomes will include routinely collected delivery and pregnancy outcomes as well as patient-reported outcomes collected via online questionnaires at the commencement and completion of the program (anthropometrics, and behavioral and psychosocial factors). If a participant does not complete these assessments online, a follow-up telephone call will be completed by study staff to gather information via the telephone.

Table 1. Primary and secondary outcomes, assessment tools, and RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) framework indicators.

RE-AIM indicator and description of outcome	Collection method/assessment tools
Reach and representativeness (primary outcome)	
Percentage of eligible women referred	Administrative data
Percentage of referred women taking up the service	Administrative data
Number of sessions attended	LWdP ^a program REDCap ^b database
Participant characteristics	LWdP program REDCap database
Implementation (primary outcome)	
Completion of pre- and postprogram assessments	Questionnaires
Staff survey	Questionnaires
Completion rates	LWdP program REDCap database
Withdrawal rates	Medical records and LWdP program REDCap database
Reasons for withdrawal	Questionnaire
Coaching call fidelity	Self-assessment database
Interventionist characteristics and allocated participants	Staff administrative database
Implementation strategies	Mapped to Expert Recommendations for Implementing Change (ERIC) strategies [35]
Adoption and maintenance (primary outcome)	
Referral source and number of referrals	Medical records and administrative data
Staff survey	Questionnaire
Adherence to implementation protocol	LWdP program REDCap database
Effectiveness (secondary outcome)	
Anthropometric outcomes	
Weight, height, BMI	Medical records and self-reports
Gestational weight gain	Medical records, classified according to Institute of Medicine recommendations [2] (adjusted to 36 weeks)
Behavioral outcomes	
Dietary intake	Fat and fiber behavior questionnaire [36]
Physical activity	Active Australia Survey [37]
Sedentary behavior	International Physical Activity Questionnaire [38]
Psychosocial outcomes	
Delivery and pregnancy outcomes	
Gestational diabetes mellitus (diagnosed according to the Queensland Health Clinical Guideline for Gestational diabetes mellitus [40]); pregnancy-induced hypertension (excluding pre-eclampsia and HELLP); pre-eclampsia; mode of delivery; delivery complications; birth weight: macrosomia (>4000 g) and large for gestational age (>90th percentile based on Australian population [41]); neonatal morbidity, treatment, and admission to special or intensive care	Medical records
Participant satisfaction	Semiquantitative survey
Staff satisfaction	Semiquantitative survey
Cost	Hospital financial and outcome records

^aLWdP: Living Well during Pregnancy.

^bREDCap: Research Electronic Data Capture.

Withdrawal Rates and Reasons

Women who withdraw from the program after receiving at least one coaching call will be sent a text message with a link to a short electronic survey. This anonymous survey will evaluate satisfaction with the program and reasons for program withdrawal.

Staff Survey

The understanding and acceptability of the program by staff (including clinicians and administrative personnel) will be assessed via a survey 2 months prior to completion of the evaluation period. Both electronic and paper-based surveys will be available. Electronic links to the online survey will be disseminated to staff from line managers. Paper-based surveys will be available in staff lunchrooms with collection boxes available for return of the survey. Administrative staff will be asked about referral and booking processes, whereas clinicians will be asked about their referral practices, program understanding, and barriers to referral. Survey responses will be provided on a 5-point Likert scale.

Dietary Intake and Behavior

The fat and fiber behavior questionnaire (FFBQ) is a 20-item questionnaire used to assess dietary behaviors (frequency of consumption, use of food items, and food categories) that has been validated against a food frequency questionnaire in the adult Australian population and is able to detect changes in fiber and fat-related intake behaviors [36]. It provides information on general food patterns rather than specific energy and macronutrient intake. Nine items relate to the frequency of consumption of particular high-fat or high-fiber foods, measured on a 5-point Likert scale (ranging from 5=never to 1=6 or more days per week). Nine items ask about behaviors related to cooking, eating, or choosing foods, such as type of dairy products or bread, measured on a 5-point Likert scale (ranging from 1=never to 5=always) with a “not applicable or do not know” option for those who do not eat a particular food or are not aware of specific cooking methods [36]. Two items assess the number of servings of fruits (1 item) and vegetables (1 item) consumed each day [36]. These 2 items contribute to the fiber and total FFBQ scores and are also valid stand-alone measures of fruit and vegetable intake [42]. The FFBQ is easy to score and administer, provides a good alternative to food frequency questionnaires in interventions, and has been used previously with pregnant women [20].

The Intuitive Eating Scale-2 is a 23-item tool that measures individuals' tendency to follow their physical hunger and satiety cues when determining when, what, and how much to eat [39]. Participants select the option that best describes their attitude or behavior to each item rated on a 5-point Likert scale (ranging from 1=strongly disagree to 5=strongly agree).

Physical Activity and Sedentary Behavior

The Active Australia Survey consists of 8 questions designed to assess the frequency and duration of walking and performing moderate and vigorous physical activity in the past week [37]. The total number of sessions and minutes of physical activity will be treated as continuous variables. Values greater than 840 minutes will be recoded to this value to avoid over-reporting in

accordance with recommendations for use of survey items [23]. A single item from the International Physical Activity Questionnaire [38] will assess sedentary time. This item assesses the total duration of sitting time on a weekday in the past 7 days [38]. These questionnaires will all be administered electronically and verified by the dietitian.

GWG

Pregnancy weight data have been collected routinely at the study hospital since 2015. GWG will be calculated by subtracting self-reported prepregnancy weight from weight recorded at 36 weeks' gestation [43]. Self-reported prepregnancy weight has been demonstrated to be an accurate depiction of weight at conception for most women [44]. For women who deliver prior to their 36-week appointment, the last recorded weight will be used to estimate GWG and will be adjusted for in multiple variable analysis. GWG will be categorized as inadequate, within range, or excessive according to prepregnancy BMI ranges recommended by the IOM [2] and adjusted for the 36-week measure.

Analysis

Economic Evaluation

An economic analysis from a health services perspective will be conducted following the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines for modeling [45]. The fixed costs of implementing the LWdP program (ie, expenditures required to deliver the program and train dietitians in health coaching) will be documented. Dollar values will be assigned to these resources using publicly available information such as appropriate salary rates for the time of personnel involved in the above activities and commercial costs for the production of any training materials and program booklets. Fixed costs will be allocated equally over all participants who consented to participate in the program. Variable costs (ie, those that are proportional to the volume of service provided) will be allocated in proportion to the stage of the program reached by individuals [46].

The costs of different birth outcomes will be determined from the Royal Brisbane and Women's Hospital's unit costing based on the previous 12 months of administrative data covering all births occurring in this time frame. Costs will be stratified by BMI category and gestational diabetes status. As cost data of this nature generally have asymmetric distributions and heteroskedastic errors [47], an appropriate statistical model (eg, generalized linear model, generalized linear mixed model, or generalized estimating equation) for comparing the costs of birth by gestational diabetes status will be determined once the underlying distribution and quality of the data are assessed. As quality of life is not measured within the trial or available in the preintervention administrative data, utility weights will be assigned to birth outcomes using relevant literature sources [48,49].

A cost-utility analysis will be undertaken with the primary analysis from the perspective of the health care system. This perspective is the most commonly used economic evaluation method in Australia for policy makers [50] and will allow comparisons across other sectors to identify the relative

cost-effectiveness of the intervention for funding proposals. An incremental cost-effectiveness ratio (ICER) will be calculated using the following formula:

$$\frac{int - usual}{QALY}$$

where *int* is the new intervention, *usual* represents usual care, and *QALY* stands for quality-adjusted life-year.

The model will include sensitivity analysis of key parameters, and outputs will include cost-effectiveness acceptability curves; these will display the probability of cost-effectiveness at varying thresholds of net monetary benefit.

Statistical Analysis

Primary (program implementation) outcomes (reach, uptake, and retention) will be reported descriptively and compared with the outcomes of a retrospective face-to-face comparison group. Where corresponding data are available for any secondary outcomes (such as GWG), results from the retrospective group will be compared with those of the prospective group. Chi-square and independent sample *t* tests will compare outcomes between retrospective and prospective groups. Analyses of secondary (program effectiveness) outcomes in the prospective group will be by mixed models, which will allow for repeated measures (baseline and follow-up) and include all participants with baseline data (including those with missing data at follow-up), with adjustment for predictors of dropouts to minimize selection bias. The relationship between intervention dose (number of calls received) and secondary behavioral and clinical outcomes will be examined. The optimal model will be selected using both indices of fit and model interpretability and parsimony. Outcomes will be reported as per protocol and intention-to-treat. Per protocol is defined as any participant who completed 4 or more telephone counseling sessions. Sensitivity of conclusions to missing data assumptions will be evaluated.

Results

The LWdP program commenced in February 2018. The prestudy period for retrospective data inclusion was from October 2016 to October 2017 and includes data from 49 women. The poststudy period for data collection commenced when the program was initiated in February 2018 and the last included participant for data analysis was enrolled in August 2019. A total of 152 women consented to have their data included in the poststudy period. Data collection of all variables was finalized in December 2020. Data cleaning has commenced and data analysis will be completed by June 2021.

Discussion

Gaining too much weight in pregnancy is an issue in Australia and occurs more frequently with women who begin their pregnancy above a healthy weight [1,6]. Although dietary counseling and weight monitoring are effective in reducing excessive GWG [34], intensive support is needed for those who experience significant barriers to achieving healthy weight gain

[29]. While the evidence for pregnancy weight management interventions exists [34], translating evidence into usual antenatal care services is challenging. Furthermore, traditional face-to-face models of care are typically poorly attended and provide many women with an additional barrier to accessing support.

The LWdP telephone counseling program is aimed at supporting women at high risk of excessive weight gain during pregnancy to achieve GWG within the recommendations. Dietetic counseling will be used to promote healthy eating and physical activity, consistent with the Australian dietary guidelines, during 10 telephone coaching calls. This paper presents a pragmatic implementation and evaluation of the LWdP program to reduce excessive GWG using the RE-AIM evaluation framework to determine considerations for dissemination, scalability, and sustainability. This study will extend the current knowledge base that telephone counseling is cost-effective and results in desired behavior changes in many other adult populations [17,28], adding evidence regarding cost-effectiveness and feasibility in a population at risk of excessive GWG, as well as document clinical effectiveness when delivered through routine antenatal care. Furthermore, the incorporation of a full economic analysis will allow the relative costs and benefits of this program to be assessed. This information is important to funders and policy makers to understand the implications of scaling up the intervention.

A potential limitation of the study is that it will be delivered at a single (Queensland) institution. However, it is hoped that with 6% of the approximately 68,000 Queensland births taking place at this hospital each year and the hospital's antenatal population being generally representative of the state's demographics [1], the generalizability of the study findings will be increased. The evaluation metrics gathered through the RE-AIM framework will inform future adoption and dissemination considerations to other centers with a different resourcing context. Further, while the use of a retrospective control group and change-over-time design introduces limitations in data interpretation when compared with a randomized controlled trial, applying a pragmatic implementation approach provides a logical, "real-world" approach that is useful in health service research and implementation science. Additionally, the reliance on the self-reported prepregnancy weight and nutrition intake and physical activity measures, as well as self-reported fidelity adherence to the dietitian coaching calls, introduces the potential for recall bias and, hence, biased analyses. This is a common concern for GWG, nutrition, and physical activity studies, but given the purpose, size, and budget of this study, more detailed assessments were not considered feasible. Importantly, the study's strengths include the applied nature of the implementation, robust health services data available, and integration into routine care. By evaluating the implementation of an evidence-based intervention into routine health service delivery will provide the practice-based evidence needed to inform decisions about its incorporation into routine antenatal care.

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Authors' Contributions

SdJ in consultation with EE devised the study, adapted the LWdP program from the Healthy Living after Cancer project, and selected the methods. SdJ wrote the initial protocol and prepared the final manuscript for submission. TG assisted in developing data collection tools, contributed to the methods, and provided feedback on the final manuscript. HP contributed to data collection and implementation of the LWdP program. NM contributed to the analytical plan and reviewed, edited, and contributed to the final manuscript. TC and ATC provided input on economic analysis and reviewed the final manuscript. LC contributed to study design and reviewed manuscript drafts. EE and SW provided advice on implementation science processes and evaluation, contributed to the methods and discussion, and provided critical feedback on manuscript drafts.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Living Well during Pregnancy intervention content mapped to the taxonomy of behavior change techniques (v1).

[DOCX File, 22 KB - [resprot_v10i3e27196_app1.docx](#)]

Multimedia Appendix 2

Intervention phases, call frequency, and call objectives of the Living Well during Pregnancy telephone counselling program.

[DOCX File, 15 KB - [resprot_v10i3e27196_app2.docx](#)]

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Abbreviations

- ERIC:** Expert Recommendations for Implementing Change
- FFBQ:** fat and fiber behavior questionnaire
- GWG:** gestational weight gain
- ICER:** incremental cost-effectiveness ratio
- IOM:** Institute of Medicine
- ISPOR:** International Society for Pharmacoeconomics and Outcomes Research
- LWdP:** Living Well during Pregnancy
- RE-AIM:** Reach, Effectiveness, Adoption, Implementation, and Maintenance
- REDCap:** Research Electronic Data Capture

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Protocol

Association Between a Low Carbohydrate Diet, Quality of Life, and Glycemic Control in Australian Adults Living With Type 1 Diabetes: Protocol for a Mixed Methods Pilot Study

Janine Paul^{1,2}, BHumanMvt, GradCertDiabEd, MSc; Rati Jani², PhD; Peter Davoren¹, MD; Catherine Knight-Agarwal², PhD

¹Diabetes and Endocrinology, Gold Coast University Hospital and Health Service, Southport, Australia

²Faculty of Health, University of Canberra, Bruce, Australia

Corresponding Author:

Janine Paul, BHumanMvt, GradCertDiabEd, MSc
Diabetes and Endocrinology
Gold Coast University Hospital and Health Service
1 Hospital Boulevard
Southport, 4215
Australia
Phone: 61 7 5687 4779 ext 74779
Fax: 61 7 5687 4399
Email: u3189207@uni.canberra.edu.au

Abstract

Background: Globally, the prevalence of type 1 diabetes mellitus (T1DM) is rising. In 2020, a total of 124,652 Australians had T1DM. Maintaining optimal glycemic control (hemoglobin A_{1c} ≤7.0%, ≤53 mmol/mol) on a standard carbohydrate diet can be a challenge for people living with T1DM. The Diabetes Complications and Control Trial established that macrovascular and microvascular complications could be reduced by improving glycemic control. Recent studies have found that a very low or low carbohydrate diet can improve glycemic control. However, the overall evidence relating to an association between a very low or low carbohydrate diet and glycemic control in people living with T1DM is both limited and mixed. In addition, research has suggested that a reduced quality of life due to anxiety and depression adversely influences glycemic control. Despite a potential link between a very low or low carbohydrate diet and optimal glycemic control, to our knowledge, no research has examined an association between a low carbohydrate diet, quality of life, and glycemic control, making this study unique in its approach.

Objective: The study aims to develop a validated diabetes-specific quality of life questionnaire for use in Australian adults with T1DM and to determine if an association exists between a low carbohydrate diet, quality of life, and glycemic control in Australian adults living with T1DM.

Methods: This cross-sectional study will be conducted in a tertiary hospital outpatient setting and will consist of 3 phases: phase 1, online Australian diabetes-specific quality of life questionnaire development and piloting (25-30 adults with T1DM); phase 2, questionnaire validation (364 adults with T1DM); and phase 3, a 12-week dietary intervention to determine if an association exists between a low carbohydrate diet, quality of life, and glycemic control in adults with T1DM (16-23 adults with T1DM). The validation of the study-developed Australian diabetes-specific quality of life questionnaire, and changes in hemoglobin A_{1c} and quality of life in adults with T1DM while undertaking a low carbohydrate diet over 12 weeks will be the primary outcomes of this study.

Results: Phase 1 of the study is currently open for recruitment and has recruited 12 participants to date. It is anticipated that the first results will be submitted for publication in November 2021. Presently, no results are available.

Conclusions: This study is the first of its kind in that it will be the first to generate a new validated instrument, which could be used in evidence-based practice and research to understand the quality of life of Australian adults with T1DM. Second, the low carbohydrate dietary intervention outcomes could be used to inform clinicians about an alternative approach to assist T1DM adults in improving their quality of life and glycemic control. Finally, this study could warrant the development of an evidence-based low carbohydrate dietary guideline for adults living with T1DM with the potential to have a profound impact on this population.

Trial Registration: ClinicalTrials.gov NCT04213300; <https://clinicaltrials.gov/ct2/show/NCT04213300>

International Registered Report Identifier (IRRID): PRR1-10.2196/25085

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KEYWORDS

type 1 diabetes; diet; low carbohydrate; HbA_{1c}; adults; quality of life

Introduction

There are more than 420 million people worldwide, aged 20 to 79 years, living with type 1 diabetes mellitus (T1DM) [1]. In 2020, a total of 124,652 Australians had T1DM [2]. As the number of people with this autoimmune condition increases, so does the prevalence of those with suboptimal glycemic control [3].

Glycemic control is evaluated by glycated hemoglobin (HbA_{1c}), which provides an average blood glucose level over a period of 2 to 3 months [4]. The target for optimal glycemic control for people with T1DM is $\leq 7.0\%$ (≤ 53 mmol/mol) [5]. In 2015, data from T1DM registries from 19 countries across Europe, North America, and Australasia (N=324,501) showed that only 46% of adults (aged ≥ 25 years) with T1DM achieved the HbA_{1c} target of $< 7.0\%$ [6].

Suboptimal glycemic control increases the risk of development and progression of various diabetes-related complications including hypoglycemia, diabetic ketoacidosis neuropathy, nephropathy, retinopathy, and cardiovascular disease [1].

The Diabetes Control and Complications Trial aimed to determine the long-term frequency and severity of chronic complications in individuals living with T1DM using intensive insulin therapy with the goal of maintaining blood glucose levels as close to normal range as possible. This seminal work convincingly demonstrated the effectiveness of intensive insulin therapy in reducing the long-term complications of T1DM and improving the prospects for a healthy life span for individuals living with T1DM. This landmark study established the glycemic control guidelines used today [7].

A recent systematic review reported the incidence and prevalence of diabetic ketoacidosis in adults with T1DM from 3 continents [8]. In this review, 19 studies (1 randomized control trial and 18 cross-sectional studies) containing similar numbers of males and females, were included, with over 80% of participants being White. The review found that adults aged 18 to 25 years had the highest prevalence of diabetic ketoacidosis (100-120 cases per 1000 in studies with 12 months' recall) compared to those older than 65 years who had the lowest prevalence of diabetic ketoacidosis (38-60 cases per 1000 in studies with a 12-month recall) [8].

Traditionally, it has been recommended that people living with T1DM consume 45% to 60% of total energy intake from carbohydrate sources [9]. Dietary approaches commonly used to manage glycemic control include carbohydrate counting, which matches insulin-to-carbohydrate intake, and/or a low glycemic index diet [10,11].

Recently, there has been a growing focus on the utility of a low carbohydrate diet to manage glycemic control in individuals

living with T1DM [12,13]. This dietary management strategy has been thoroughly investigated in people living with type 2 diabetes mellitus (T2DM) [14,15]. However, there is a paucity of evidence regarding T1DM.

A very low carbohydrate diet is defined as 0-50 g per day or $< 10\%$ of the total daily energy intake [16], while a low carbohydrate diet is defined as < 130 g per day or $< 26\%$ of the total daily energy intake [16,17]. Schmidt et al [12] conducted a randomized crossover study to examine the effects of a low carbohydrate diet (< 100 g carbohydrate/day) compared to a high carbohydrate diet (> 250 g carbohydrate/day) on glycemic control. Participant baseline characteristics included White adults from Denmark (male: 6/14, 43%; female: 8/14, 57%; 14 with T1DM; mean age 44 years, SD 12 years). Participant median diabetes duration was 19 (range 13-32) years, and the HbA_{1c} was 7.5% (range 7.2%-7.6%). Participants undertook two, 12-week interventions separated by a 12-week "washout" period, with 10 of the 14 participants completing the study. The study found that a low carbohydrate diet compared to a high carbohydrate diet did not significantly improve HbA_{1c}, but did stabilize glucose variability and reduce hypoglycemia frequency ($P < .001$) [12].

There is only 1 systematic review that has examined the association between very low and low carbohydrate diets and glycemic control in people living with T1DM [18]. It included a total of 9 original studies: 2 randomized controlled trials [19,20], 2 quasi pre- or post-cross-sectional [21,22] studies, 4 case series [23-26], and 1 case report [27]. Participants ranged from 14 to 65 years of age and resided in the United Kingdom, the United States, Europe, Australia, or New Zealand. Fewer than half the studies (3/9) reported a significant improvement in HbA_{1c} (0.7%-2.4%; $P < .05$) [18]. The difference in sample sizes, study methodologies, and participant baseline characteristics (age, gender, ethnicity, and diabetes duration) may account for these nonsignificant results. Despite a paucity of evidence, associations have been observed between very low and low carbohydrate diets with good glycemic control in individuals living with T1DM [13,19,23-26]. However, these findings are relatively mixed [12,13,19,21,23-26,28-31].

Very little research has been conducted in the area of a low carbohydrate diet and quality of life (QoL) in adults living with T1DM. Additional research is needed to determine if there is a link between these 2 variables because T1DM has been reported to be the cause of a reduced QoL [32]. Roy and Lloyd [33] conducted a systematic review to examine the evidence for rates of depression within the diabetes population. The authors reported the prevalence of depression to be 3 times higher in people living with T1DM when compared to those without it (12% vs. 3%, respectively). In Australia, it has been found that 41% of adults (> 18 years old) living with T1DM experience

diabetes-related anxiety, depression, and stress [34]. In turn, these psychological issues have been linked with suboptimal glycemic control and diabetes complications, thus contributing to diminished QoL.

There is no agreed explanation of QoL [35,36] as demonstrated by the numerous existing definitions reported in the literature [36-40]. There is however, universal agreement that QoL is a multidimensional, subjective construct that includes at least three domains: physical (eg, pain), psychological (eg, body image), and social (eg, relationships) well-being [35-37,41-44]. Common QoL definitions do not appear to use a holistic lifestyle approach and fail to consider dietary well-being, a key aspect of QoL for individuals living with T1DM [45].

QoL is commonly assessed in T2DM populations [46,47] but rarely in adults living with T1DM [48]. Pereira et al [47] conducted a systematic review to determine the relationship between QoL and HbA_{1c} in those living with T1DM. The review consisted of 110 studies (78 observational and 32 interventional) from countries in North America and Europe, and included 69 T1DM studies, 35 T2DM studies, and 6 T1DM and T2DM studies. All studies included an approximately 1:1 male to female participant ratio, with an age range from 5 to 70 years and a diabetes duration from 2 to 29 years. QoL instruments used included the Diabetes Quality of Life Measure (DQOL) [49] and the Diabetes Quality of Life for Youth (DQOLY) measure [50]. Baseline HbA_{1c} for T1DM interventional and observational studies ranged from 6.1% to 11.0% and from 7.0% to 12.2%, respectively. Endpoint HbA_{1c} ranges for interventional and observational studies were reduced from 5.9% to 9.5% and from 7.1% to 9.6%, respectively. Despite a reduction in HbA_{1c}, only 41% of participants reported an improvement in QoL, suggesting that people living with T1DM generally perceive this as unsatisfactory [47].

The Diabetes-Specific Quality of Life Scale (DSQOLS) is the only validated QoL instrument for adults living with T1DM [48]. Nevertheless, it is not suitable for assessing the dietary well-being of Australian adults because the instrument fails to consider carbohydrate counting, which is a fundamental skill used by those living with T1DM in Australia to manage insulin and blood glucose levels [51]. The instrument also neglects to assess food intake satisfaction, which is another important aspect of dietary well-being [45]. These factors are likely to influence QoL outcomes; therefore, the development of a new T1DM-specific QoL instrument that includes the four domains of physical, psychological, social, and dietary well-being is being proposed.

To address the identified deficit in the literature, our study aims to develop and validate a diabetes-specific QoL questionnaire for use in Australian adults with T1DM and to determine if an association exists between a low carbohydrate diet, QoL, and glycemic control.

Methods

Study Design and Ethics

This cross-sectional study will be conducted in 3 phases. Study phase 1 will include online Australian diabetes-specific QoL questionnaire development and piloting. Study phase 2 will consist of Australian diabetes-specific QoL questionnaire validation with the following 2 subphases: subphase 2a, which will include initial validation with an online diabetes-specific QoL questionnaire; study subphase 2b, which will include online questionnaire validation of the Australian diabetes-specific QoL, the Medical Outcomes Study 36-Item Short Form Health Survey (MOS SF-36), DQOL, and Problem Areas in Diabetes (PAID-20) questionnaires; study phase 3 will include intervention, which will be aimed at determining if an association exists between a low carbohydrate diet, QoL, and glycemic control in adults living with T1DM.

Ethics approval has been obtained from the Gold Coast Hospital and Health Service (GCHHS) Human Research Ethics Committee (HREC) and the University of Canberra HREC. Ethics approval numbers for study phase 1 and 2 are HREC/2019/QGC/54049 and HREC/2019/UC/2223, respectively. The approval numbers for study phase 3 are HREC/2019/QGC/60717 and HREC/2020/UC/4691. The study was registered at ClinicalTrials.gov (NCT04213300).

Participant Recruitment

Participant recruitment for each study phase will be facilitated by both face-to-face and online (eg, social media and email) approaches. Information posters will be placed across the GCHHS patient waiting areas containing the principal investigator's (JP) contact details (email, phone number) and a questionnaire QR (quick response) code.

Study Outline

First, approval for the study was gained from the Gold Coast Hospital and Health Service (GCHHS) HREC and the University of Canberra HREC.

Study Phase 1

Study phase 1 will consist of the development and piloting of the online Australian diabetes-specific QoL questionnaire. In all, 25-30 adults (≥18 years old) with T1DM will be included. Data will be collected via an online questionnaire (10-15 minutes) followed by a face-to-face or online interview (20-30 minutes), with the period of data collection lasting 1 month. The face-to-face or online interview location will be the Gold Coast University Hospital, Outpatient Department, Diabetes Resource Centre or the Zoom online platform (the participants may choose their preferred interview method), respectively. Interview data will be audio-recorded, transcribed verbatim, coded, and parsed for common themes. A summary of key suggestions for revising the online questionnaire to be used in study subphases 2a and 2b will be produced.

Study Phase 2

Study phase 2a will be the initial validation of the online Australian diabetes-specific QoL questionnaire. In all, 364 adults

(≥ 18 years old) with T1DM will be included. Data will be collected via an online questionnaire (estimated completion time 10-12 minutes). Participants will have access to the questionnaire for 2 weeks. If the questionnaire link expires, the participant may request a new link by contacting JP. The data collection period for this phase will last 3 months.

Study phase 2b will consist of subsequent validation of the Australian diabetes-specific QoL questionnaire using the MOS SF-36, the DQOL, and the PAID-20 questionnaires. Three months after study subphase 2a is completed, study subphase 2b will commence. Participants from study subphase 2a will be invited by email to complete the same online questionnaire for a second time. In addition, they will be asked to complete the MOS SF-36 [52], DQOL [49], and the PAID-20 [53] questionnaires. Responses will be analyzed to determine the statistical reliability and validity of the Australian diabetes-specific QoL questionnaire. In all, 100 adults (≥ 18 years old) with T1DM will be included. Data will be collected via an online questionnaire (estimated completion time 15-18 minutes). Participants will have access to the questionnaire for 2 weeks. If the questionnaire link expires, the participant may request a new link by contacting JP. The data collection period for this phase will last 3 months.

Study Phase 3

Study phase 3 will comprise preintervention, intervention, and postintervention procedures. The overall aim of this phase is to determine if an association exists between a low carbohydrate diet, QoL, and glycemic control in adults living with T1DM through use of a cross-sectional cohort study. In all, 16-23 adults (≥ 18 years old) with T1DM will be included.

The preintervention period will begin 1 week prior to commencing the intervention procedure. Participants will attend the study hospital for approximately 3 hours to do the following: complete the study consent form (hard copy), if not already completed; discuss the intervention process ensuring they have a clear understanding of what is required during all phases of the intervention; receive an information kit containing the study procedure, the research team (endocrinologist [PD], credentialed diabetes educator [CDE; DI], and diabetes dietitian [JP]) and Gold Coast Hospital Emergency Department contact details, a food diary, a sick day management plan, and support services (in case any psychological distress is experienced during the study); complete the online Australian diabetes-specific QoL questionnaire; have weight (kg), height (cm), and glycated hemoglobin (HbA_{1c}) recorded; receive continuous glucose monitoring system (CGMS) education and supply of CGMS equipment; apply the CGM sensor to their abdominal wall, attach the transmitter, and establish a connection between the transmitter and their own compatible smart device in order to enable recording and displaying of their glucose levels; and receive instruction on how to continue with their usual, daily routine, and be asked to commence recording what they eat and drink via a food diary. The day prior to commencing the intervention, participants will receive their individualized meal plans by email.

The intervention procedure will take place in the participants own environment and last 12 weeks. Participants will be

expected to perform the following during the intervention period: follow the low carbohydrate dietary plan (dietary composition: 20% carbohydrate [< 100 g], protein 25%, and fat 55%) as prescribed by a diabetes dietitian, complete a daily food diary, test blood ketone levels weekly (at fasting), participate in a weekly endocrinologist appointment to discuss blood glucose levels and insulin adjustments by telephone, attend the diabetes dietitian appointment by telephone to discuss any concerns with the dietary plan, contact DI if having problems with the CGMS, and change the CGM sensor every 10 days.

The postintervention procedure will begin the day after the intervention has been completed, and participants will attend the study hospital for up to 90 minutes for the following: to record weight (kg) and HbA_{1c} with DI, to complete the online diabetes-specific QoL questionnaire and online patient global impression change questionnaire, and to participate in a face-to-face CGMS experience interview with JP.

Participant Eligibility Criteria

Inclusion Criteria

Study participants for each phase will self-identify against the following eligibility criteria: aged ≥ 18 years, living with T1DM, and T1DM diagnosis for ≥ 1 year. Study phase 3 includes 5 additional eligibility criteria that participants must meet: (1) use of multiple daily injections for insulin administration, (2) experience of at least one hypoglycemic episode since diagnosis, (3) knowledge of hypoglycemic management, (4) ability to test for blood ketones, and (5) knowledge of blood ketone management.

Exclusion Criteria

Ineligible participants will include the following: people living with T2DM; people living with gestational diabetes mellitus; people who administer insulin using a continuous subcutaneous insulin infusion; those living with a known food allergy; those with a history of an eating disorder; those with a BMI < 18.5 kg/m²; those aged < 18 years; those who are pregnant or planning to conceive; those taking prescription medications, such as phentermine or corticosteroids; individuals with an active medical problem, such as a recent myocardial infarction, stroke or peripheral revascularization (within 3 months), active treatment of diabetic retinopathy, or recent serious infection (requiring in-hospital treatment or prolonged antibiotic therapy), that may hinder their ability to take part or may potentially affect study outcomes; those for whom written materials may be unsuitable (eg, vision-impaired or illiterate individuals); those unable to understand English; and those who fail to sign the participant consent form.

Sample Size

Study Phase 1: Online Australian Diabetes-Specific QoL Questionnaire Development and Piloting

Sample size data will be collected from approximately 25-30 adult participants with T1DM. This sample size is based on previous research [54] and has been deemed as sufficient to facilitate in-depth face-to-face interviews [55].

Study Phase 2: Online Australian Diabetes-Specific QoL Questionnaire Validation

This phase will include 2 subphases: 2a and 2b. Subphase 2a will involve initial validation. This will include the online Australian diabetes-specific QoL questionnaire and will require 364 adult participants with T1DM. This sample size has been calculated using the participant-to-item ratio method [56]. Subphase 2b will involve subsequent validation. This will include the online Australian diabetes-specific QoL, MOS SF-36, DQOL, and PAID-20 questionnaires, and will require 100 responses to be collected for test-retest, convergent, and divergent validity statistical analysis. This sample size is based on biostatistician advice and other studies that have validated QoL instruments [49,57-59].

Study Phase 3: The Low Carbohydrate Dietary Intervention

A sample size of 16 has been calculated with a 0.05 significance level and power of 0.8 to detect a significant clinical difference of 1.0% in HbA_{1c}. A 1.0% change in HbA_{1c} will be used because dietary changes alone have shown to improve HbA_{1c} by 1.0% [60]. To complete the study, 16 participants are required. To account for a 40% attrition rate [12], 23 participants will be the maximum number recruited.

Data Privacy and Confidentiality

Confidentiality and privacy of participant data will be restricted to JP. The strategy for identification, coding, and deidentification of participant data will involve recording the participants' name, email address, and contact phone number in an electronic master

list stored at the hospital and retained for archiving purposes. All questionnaires in this study will be delivered using an online encrypted questionnaire platform to ensure participant responses are secure and confidential.

Data Collection

Study Phase 1: Online Australian Diabetes-Specific QoL Questionnaire Development and Piloting

Volunteering participants will consent to completing both the online questionnaire and a face-to-face interview. Table 1 outlines each questionnaire section and provides a brief description of what is included. The participants' pilot questionnaire link will be active for 2 weeks. A courtesy email reminder will be sent to those who have not completed or have partially completed the pilot questionnaire after 7 days. It is anticipated that the questionnaire will take 10-15 minutes. Once the pilot questionnaire is completed, the participant will be contacted via phone to arrange a suitable time for either a face-to-face interview at the study hospital or an online interview. It is estimated that the duration of the interview will be 20-30 minutes. Interviews will be undertaken by JP with the aid of a question guide to ensure a consistent approach is followed. Each interview will be audio-recorded and then transcribed verbatim. Common participant feedback will be documented and then reviewed by the research team. This feedback will be used to modify specific items identified as needing improved clarity and concision or to remove them due to irrelevance. The revised version of the online questionnaire will be used in study phase 2, and subphases 2a and 2b.

Table 1. Study phase 1: online Australian diabetes-specific quality of life questionnaire completed by adults with type 1 diabetes mellitus (n=25-30).

Questionnaire section	Brief description of items	Source
Section 1: information sheet ^a	Overview of the study	N/A ^b
Section 2: screening questions ^c	Assessment of study eligibility	N/A
Section 3: consent form ^a	Signed by participant	N/A
Section 4: Australian diabetes-specific quality of life questions ^d	A 28-item questionnaire containing 4 constructs measuring diabetes quality of life using a 10-point Likert scale from "very strongly disagree" to "very strongly agree"	Adapted from [48,57]
Section 5: sociodemographic covariates	Data collection: gender, age, height, weight, diabetes duration, occupation, level of education, etc	Adapted from [61-63]

^aParticipant information and consent form are to be completed online.

^bN/A: not applicable.

^cScreening questions are to be completed online. The response to each question is yes or no. The questions include the following: "I have type 1 diabetes mellitus," "I am 18 years or older," and "I have had type 1 diabetes mellitus for one year or longer."

^dAustralian diabetes-specific quality of life questions were developed using previously validated questionnaires [48,57]; input will be collected by the research team through one-to-one participant interviews.

Study Phase 2: Online Australian Diabetes-Specific QoL Validation

Study phase 2 will be split into 2 subphases (2a and 2b). Study subphase 2a will consist of initial validation using the online Australian diabetes-specific QoL questionnaire. Data will be collected from 364 participants to support the statistical validation of the questionnaire. These 364 participants will be different to those who participated in study phase 1. Table 2

shows each questionnaire section and a brief description of the section. After 7 days, a reminder email will be sent to those participants who have not commenced or have only partially completed the questionnaire. It is anticipated that the questionnaire will take 10-15 minutes to complete. Study subphase 2b will consist of the subsequent validation using the online Australian diabetes-specific QoL, MOS SF-36, DQOL, and PAID-20 questionnaires. All participants (N=364) from

study subphase 2a will receive an email 3 months after completing the initial online questionnaire requesting the completion of the questionnaire for a second time. This email will also request the participant to complete the online MOS SF-36 [52], DQOL [49], and PAID-20 questionnaires [53].

Table 2. Study phase 2a–initial validation: online Australian diabetes-specific quality of life questionnaire completed by adults with type 1 diabetes mellitus (N=364).

Questionnaire section	Brief description of items	Source
Section 1: information sheet ^a	Overview of the study	N/A ^b
Section 2: screening questions ^c	Assessment of study eligibility	N/A
Section 3: consent form ^a	Signed by participant	N/A
Section 4: Australian diabetes-specific quality of life questionnaire	A 28-item questionnaire containing 4 constructs measuring diabetes quality of life using a 10-point Likert scale from “very strongly disagree” to “very strongly agree”	Adapted from [48,57]
Section 5: sociodemographic covariates	Data collection: gender, age, height, weight, diabetes duration, occupation, level of education, etc	Adapted from [61-63]

^aParticipant information and consent form are to be completed online.

^bN/A: not applicable.

^cScreening questions are to be completed online. The response to each question is yes or no. The questions include the following: “I have type 1 diabetes mellitus,” “I am 18 years or older,” and “I have had type 1 diabetes mellitus for one year or longer.”

Participants will be supplied with a link for access to all 4 questionnaires. Of the 364 participants, 100 participants will be needed to complete the questionnaire to establish test–retest, convergent, and divergent validity. Table 3 outlines the questionnaires to be completed as part of the subsequent validation process.

Table 3. Study phase 2b–subsequent validation: online Australian diabetes-specific quality of life, MOS SF-36, DQOL, and PAID-20 questionnaires completed by adults with type 1 diabetes mellitus (n=100).

Questionnaire section	Brief description of items	Source
Section 1: information sheet ^a	Overview of the study	N/A ^b
Section 2: screening questions ^c	Assessment of study eligibility	N/A
Section 3: consent form ^a	Signed by participant	N/A
Section 4: Australian diabetes-specific quality of life questionnaire	A 28-item questionnaire containing 4 constructs measuring diabetes quality of life using a 10-point Likert scale from “very strongly disagree” to “very strongly agree”	Adapted from [48,57]
Section 5: MOS SF-36 ^d	Measures of physical and psychological constructs of general well-being with varying response scales	[52]
Section 6: DQOL ^e	A 43-item instrument consisting of 4 constructs (satisfaction, impact, social/vocational worry, diabetes-related worry). A Likert response format from “very satisfied” to “not satisfied” for the satisfaction construct and from “never” to “always” for the other constructs.	[49]
Section 7: PAID-20 ^f	A 20-item questionnaire that measures diabetes-related distress. Each item addresses a different issue associated with diabetes. A 5-point response scale is used from “not a problem to “serious problem”.	[53]
Section 8: sociodemographic covariates	Data collection: gender, age, height, weight, diabetes duration, occupation, level of education, etc	Adapted from [61-63]

^aParticipant information and consent form are to be completed online.

^bN/A: not applicable.

^cScreening questions are to be completed online. The response to each question is yes or no. The questions include the following: “I have type 1 diabetes mellitus,” “I am 18 years or older,” and “I have had type 1 diabetes mellitus for one year or longer.”

^dMOS SF-36: Medical Outcomes Study 36-Item Short Form Health Survey.

^eDQOL: Diabetes Quality of Life Measure.

^fPAID-20: Problem Areas in Diabetes.

Phase 3: The Low Carbohydrate Dietary Intervention

Phase 3 is planned to commence in February 2021. Potential participants will volunteer to participate in the study by responding to the contact details of JP on information flyers in the hospital patient waiting areas or provided to them by an endocrinologist or CDE. Potential study participants may include those who participated in study phase 1 or 2 but may also include those who did not necessarily participate in any of the previous study phases. Potential participants who contact JP regarding study participation will have a verbal discussion to ensure they meet the inclusion criteria. Subsequently, the following study requirements for participants will be explained: following a low carbohydrate diet for 12 weeks, using a CGMS for 12 weeks, testing blood ketones weekly, completing a daily food diary, participating in 2 in-person study hospital appointments, and participating in weekly diabetes dietitian and endocrinologist telephone appointments. If the participant provides verbal consent to be included in the study, a preintervention appointment date and time will be organized with the participant to attend the study hospital 1 week prior to commencing the intervention. The participant will be sent an email to confirm the appointment date and time as well as a participant information and a consent form. The consent form may be completed and returned to JP by email prior to or at the preintervention appointment. Two days prior to the preintervention appointment, JP will telephone the participant as a courtesy reminder of the appointment date and time.

Preintervention Procedure

The preintervention appointment will be conducted by a CDE at the study hospital. The CDE will ensure the participant consent form has been completed before commencing the preintervention appointment. The CDE will discuss the study procedure to ensure the participant understands what is required during all phases of the intervention. The CDE will record the participants' weight (kg) and height (cm) using a seca 763 electronic measuring station. This information will be recorded on a participant data collection form which will be used pre- and postintervention. An HbA_{1c} test will be conducted using a DCA Vantage Analyzer (Siemens Healthineers). Participants will complete the online Australian diabetes-specific QoL questionnaire using a hospital computer. The CDE will provide each participant with a Dexcom G6 CGMS kit. The kit includes a transmitter, sensors, and a sensor applicator, as provided by Dexcom. Novice CGMS participants will be taught how to use the device. During this appointment, the participant will apply the CGM sensor to their abdominal wall, attach the transmitter, and establish a connection between the transmitter and their own compatible smart device to enable recording and displaying of their glucose levels. Participants glucose levels will then record and display glucose level via the Dexcom G6 application, which the participant will install onto their compatible smart device. The Dexcom G6 CGMS kit will be retained by the participant at the completion of the study. Participants will not use their own personal glucose monitor during the study to test blood glucose levels. However, the participant will use it weekly to test blood ketones. The participant will also be required to use their own blood ketone strips for this test.

Participants will continue with their usual, daily routine; however, they will commence recording food and fluid consumption in a food diary. Participants will be required to complete the daily food diary 1 week prior to commencing the intervention and for the 12 weeks of the intervention. The participant will email this information to the diabetes dietitian weekly to ensure these records are being maintained, as the information will be used in the final data analysis stage. Participants' individualized meal plans will be emailed to each participant the day prior to commencing the intervention. Each participant will also be provided with digital kitchen scales and measuring cups and spoons to assist with weighing and measuring foods and fluids to ensure accuracy of quantities consumed. These instruments have been supplied by the GCHHS Study, Education and Research Trust Account (SERTA).

Intervention Procedure

All participants will follow a prescribed meal plan to meet their estimated energy needs as per the Schofield formula [64]. Meal plan macronutrient distribution will be 20% carbohydrate, 25% protein, and 55% fat based on the Australian book, *The CSIRO Low Carb Diet* [65]. The meal plan contains no more than 100 g per day of dietary carbohydrate, making this intervention a low carbohydrate dietary regimen according to Feinman et al's [16] 2015 definition. Alcohol influences blood glucose levels, food and fluid choices, and quantities consumed [66]. For this reason, participants will be strongly advised to abstain from alcohol consumption during the 12-week intervention. Weekly telephone follow-up will be conducted by JP to discuss any concerns or questions participants may have. Follow-up by telephone has been shown to be an effective method to monitor medical nutrition therapy [67,68]. Weekly telephone appointments will also be conducted by the research teams' endocrinologist (PD) to discuss blood glucose level management and adjust insulin doses as needed.

Any hypoglycemia treatment will be recorded in the food diary and will detail when, what, and how much carbohydrate was used to treat the hypoglycemic event. If any hypoglycemic events occur, PD will discuss this with the participant during the weekly telephone appointment and advice will be provided to avoid future occurrences. Participants will check blood ketones once a week on the morning after an overnight fast to avoid diabetic ketoacidosis. If blood ketones are present (>0.6 mmol/l), participants will follow a "sick day" management plan, and, if unsure what to do, will contact PD for advice. Participants will be encouraged to follow their usual exercise habits, as no exercise advice will be given [69]. This study is unique, and if a participant feels they are unable to complete the 12-week intervention, they may withdraw at any time.

Postintervention Procedure

At the completion of the intervention, the participant's weight (kg) will be recorded. An HbA_{1c} test will be performed by the research teams' CDE (DI). The online Australian diabetes-specific QoL questionnaire will be readministered. An online patient global impression of change questionnaire will be administered to determine the participants' perception of the degree of change following the intervention relating to glycemic control and QoL [70]. This questionnaire will consist of 2

questions using a 7-point scale (“no change/has got worse” to “a great deal better/considerable improvement”). Finally, in an individual interview, each participant will be asked 5 questions regarding the CGMS experience relating to its acceptability, perception, benefits, and barriers. An interview question guide will be used to facilitate the interview. Data will be transcribed, coded, and parsed for common themes for inclusion in a publication.

Potential Adverse Events

Potential adverse events may include hypoglycemia, hyperglycemia, blood ketones, and diabetic ketoacidosis episodes. Any adverse events will be discussed by PD and the participant, and a plan will be put in place to prevent any future occurrences. However, adverse events are not expected to occur due to the safety alerts thresholds that will be set up on the CGM as recommended by the CGM use guidelines [71].

Outcomes

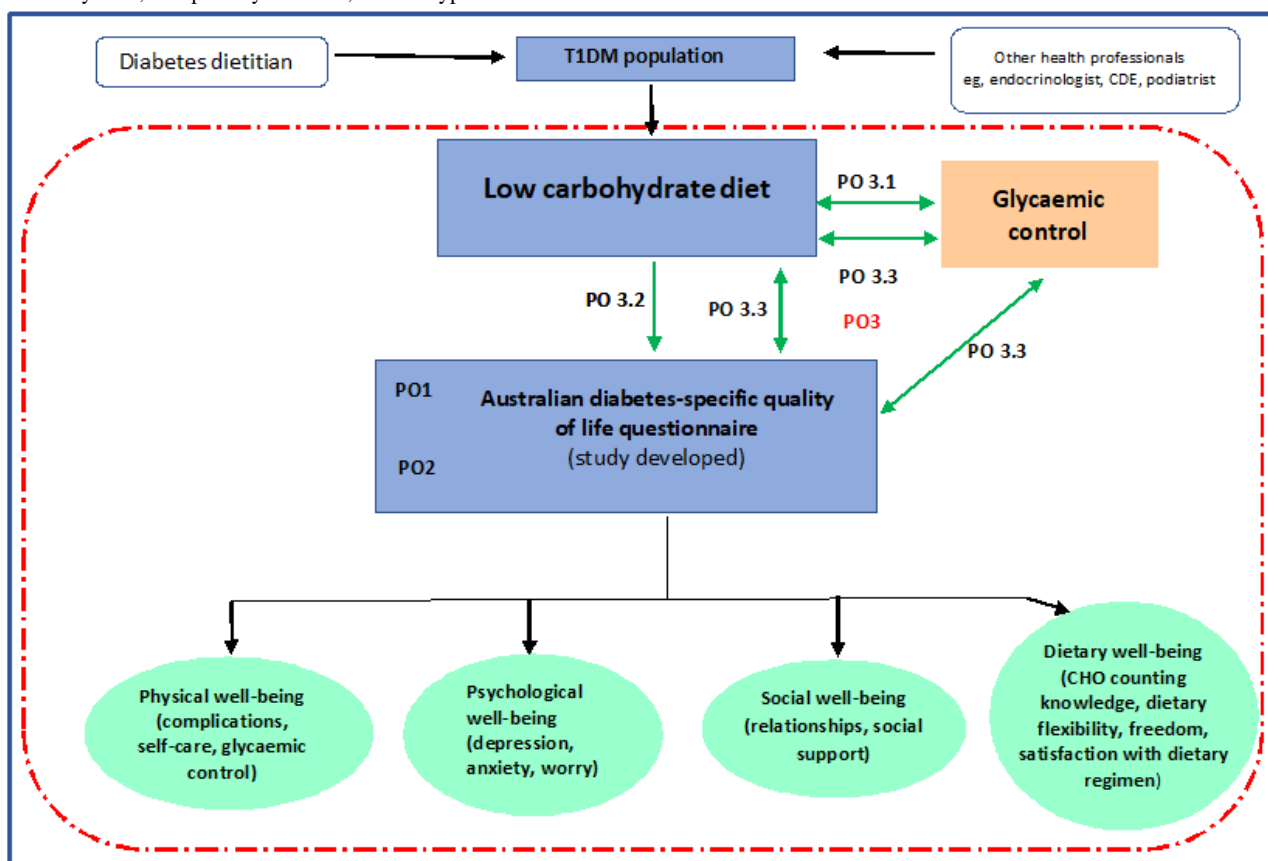
The primary outcomes will be divided according to the study phases. Primary outcome 1 will be related to the development

and piloting of the new Australian diabetes-specific QoL questionnaire in study phase 1. Primary outcome 2 will be related to the validation of the study-developed questionnaire in study phase 2. Study phase 3 will produce 3 subdeliverables that will examine the association between a low carbohydrate diet and glycemic control in adults with T1DM (primary outcome 3.1), examine the association between a low carbohydrate diet and QoL in adults with T1DM (primary outcome 3.2), and investigate whether a low carbohydrate diet mediates the relationship between QoL and glycemic control in adults with T1DM (primary outcome 3.3).

This study will have no secondary study outcomes.

Figure 1 schematically shows the relationship between the study objectives. The association between QoL, low carbohydrate diet, and glycemic control variables have been represented with double-headed arrows. This indicates that the direction of the association is unclear and may be bidirectional in nature, as each variable has the potential to influence the other [13,19,30].

Figure 1. The association between adults living with type 1 diabetes mellitus, quality of life, and glycemic control. CDE: credentialed diabetes educator; CHO: carbohydrate; PO: primary outcome; T1DM: type 1 diabetes mellitus.



Study Phase 1: Australian Diabetes-Specific QoL Questionnaire Development and Piloting

A qualitative approach will be implemented to analyze data collected from audio-recorded participant interviews. Coding will be undertaken using an interview question guide as a framework. The question guide includes the following categories: technical aspects, formatting and layout, participant

understanding of the questionnaire aim and purpose, interpretation of the questions, time taken to complete the questionnaire, and any other feedback to improve the usefulness of the questionnaire. In addition, divergence and concordance of participant opinion will be noted. Following this process, data will be cross-checked by a second CDE (trained coder). Any discrepancies will be resolved by a round table discussion

with the study team, and questionnaire items to be revised will be determined at this forum.

Study Phase 2: Online Australian Diabetes-Specific QoL Questionnaire Validation; and Study Phase 3: The Low Carbohydrate Dietary Intervention

Data will be coded, entered into a password-protected database, checked by JP, and cross-checked by the same CDE (trained coder) from study phase 1. Descriptive statistics will be reported

using mean and SD. Study phase 2 (including subphases 2a and 2b) and phase 3 data will be analyzed using R statistical software version 3.6.1 or later (R Foundation for Statistical Computing) [72]. Statistical significance will be set at a P value $<.05$.

Statistical Plan

Table 4 outlines a brief summary of the study objectives, the independent and dependent variables relating to each objective, and the planned statistical analyses to be conducted.

Table 4. Brief statistical plan.

Statistical objectives	Independent variable	Dependent variable	Statistical analysis
To develop and pilot the Australian diabetes-specific quality of life questionnaire	Australian diabetes-specific quality of life questionnaire	N/A ^a	Transcribe, code, and identify common themes in the interview data
To validate the Australian diabetes-specific quality of life questionnaire (study developed)	Australian diabetes-specific quality of life questionnaire	Factorial validation indicators: root mean square error of approximation, comparative fit index, and Tucker-Lewis index	Exploratory factor analysis, confirmatory factor analysis, and structural equation modelling
To examine the association between a low carbohydrate diet and glycemic control	Low carbohydrate diet	Glycemic control	Bivariate: ANOVA ^b and correlations. Multivariate: hierarchical regression controlling for sociodemographic covariates.
To examine the association between quality of life and a low carbohydrate diet	Low carbohydrate diet	Quality of life	Bivariate: ANOVA and correlations. Multivariate: hierarchical regression controlling for sociodemographic covariates.
To investigate whether a low carbohydrate diet mediates the relationship between quality of life and glycemic control	Low carbohydrate diet	Glycemic control and quality of life	Bivariate: ANOVA and correlations. Multivariate: hierarchical regression controlling for sociodemographic covariates.

^aN/A: not applicable

^bANOVA: analysis of variance

Results

To date, 12 participants have been recruited into phase 1 of this study. The anticipated data collection completion date for all study phases is March 2022. At present, no study results are available.

Discussion

This study is the first of its kind to examine the association between a low carbohydrate diet, QoL, and glycemic control. This cross-sectional study protocol aims to develop, pilot, and validate a diabetes-specific QoL questionnaire and determine if an association exists between QoL and glycemic control while using a low carbohydrate dietary intervention in Australian adults living with T1DM.

The strengths of this study are that, to our knowledge, no previous published research has evaluated a low carbohydrate diet and its influence on QoL and glycemic control in Australian adults living with T1DM. Moreover, this is the first study to develop and validate an Australian T1DM-specific QoL

questionnaire. Therefore, the strengths of this study are its unique approach.

The potential limitations of this study include the fact that, first, the Australian diabetes-specific QoL questionnaire is not available to those who are vision impaired, intellectually impaired, or have any other type of diabetes, such as T2DM and gestational diabetes mellitus. Future studies could develop resources to include these populations. Second, in study phases 1 and 2, questionnaire data will be self-reported and may have the potential to produce social desirability bias [73]. However, using self-reported data is the most feasible option for this pilot study in order for the sample size ($N=364$) and statistical validation of the questionnaire to be achieved. Third, study phase 3 has been designed as a nonrandomized intervention group pilot study that will inform the design and feasibility of a potential larger randomized control trial. Finally, in study phase 3, there is potential selection bias: individuals who are highly motivated to improve glycemic control are more likely to participate [25].

The Australian diabetes-specific QoL questionnaire will be a useful instrument for health care professionals, including general

practitioners, diabetes dietitians, and diabetes educators. This instrument will support health care practitioners to gain a better understanding of Australian T1DM adults' QoL perception relating to physical, psychological, social, and dietary well-being. To date, studies that have investigated the influence of a very low or low carbohydrate diet and glycemic control in adults living with T1DM have not examined QoL using a validated instrument in tandem with participants undertaking the dietary regimen [12,13,19,21,23-31]. Consequently, a validated QoL instrument is needed for clinical practice and future research to identify the QoL of Australian adults with T1DM, as no validated instrument currently exists.

It is recommended that people living with T1DM follow healthy eating dietary guidelines for the general population [3].

However, this study's dietary intervention outcomes could provide an alternative approach. Additionally, the study findings could warrant the development of a specific dietary guideline for using a low carbohydrate diet to support glycemic management and improve QoL in adults living with T1DM.

This study will generate a new validated QoL instrument which could be used in evidence-based practice and research to understand the QoL of adults with T1DM. It will also investigate the association of a low carbohydrate diet, QoL, and glycemic control in Australian adults living with T1DM. If successful, this study has the potential to have a profound impact on those living with T1DM.

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Authors' Contributions

All authors contributed to the development of the study concept. JP authored the first version of the manuscript. The manuscript was reviewed by RJ, PD, and CKA, and further revisions were made by JP.

Conflicts of Interest

None declared.

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Abbreviations

- CDE:** credentialed diabetes educator
- CGMS:** continuous glucose monitoring system
- DQOL:** Diabetes Quality of Life
- GCHHS:** Gold Coast Hospital and Health Service
- HbA_{1c}:** glycated hemoglobin
- MOS SF-36:** Medical Outcomes Study 36-Item Short Form Health Survey
- PAID:** Problem Areas in Diabetes
- QoL:** quality of life
- QR:** quick response
- SERTA:** Study, Education and Research Trust Account
- T1DM:** type 1 diabetes mellitus
- T2DM:** type 2 diabetes mellitus

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Corrigenda and Addenda

Correction: mHealth-Supported Delivery of an Evidence-Based Family Home-Visiting Intervention in Sierra Leone: Protocol for a Pilot Randomized Controlled Trial

Alethea Desrosiers¹, PhD; Carolyn Schafer¹, MPH; Rebecca Esliker², PhD; Musu Jambai³, BA; Theresa S Betancourt¹, ScD

¹Boston College, School of Social Work, Chestnut Hill, MA, United States

²University of Makeni, Makeni, Sierra Leone

³Caritas Freetown, Freetown, Sierra Leone

Corresponding Author:

Alethea Desrosiers, PhD

Boston College

School of Social Work

140 Commonwealth Avenue

Chestnut Hill, MA, 01778

United States

Phone: 1 617 552 8398

Email: alethea.desrosiers@bc.edu

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In “mHealth-Supported Delivery of an Evidence-Based Family Home-Visiting Intervention in Sierra Leone: Protocol for a Pilot Randomized Controlled Trial” (*JMIR Res Protoc* 2021;10(2):e25443) one error was noted.

In the section “Ethical Approval and Consent to Participate”, the originally published paper read:

This study received ethical approval from the relevant College Institutional Review Board and the Sierra Leone Scientific Review Committee (Multimedia Appendices 1 and 2).

However, there is no Multimedia Appendix 2 in the published paper and this sentence has been corrected to:

This study received ethical approval from the relevant College Institutional Review Board and the Sierra Leone Scientific Review Committee (Multimedia Appendix 1).

The correction will appear in the online version of the paper on the JMIR Publications website on March 10, 2021, 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

Evidence Supporting the Management of Medical Conditions During Long-Duration Spaceflight: Protocol for a Scoping Review

Kim-Anh Tran^{1,2}, MSc; Neal William Pollock^{1,2}, PhD; Caroline Rhéaume^{1,3}, MD, PhD; Payal Sonya Razdan^{1,2}, MPH; Félix-Antoine Fortier¹, MD; Lara Dutil-Fafard¹, MD; Camille Morin¹, BSc; David Pierre-Marie Monnot^{1,2}, MSc; Maxime Huot-Lavoie^{1,2}, MSc; Philippe Simard-Sauriol¹, MD; Sam Chandavong^{2,4}, BSc; Geneviève Le Pabic¹, MD; Jean-Philippe LeBlanc¹, BSc; Daniel Lafond⁵, PhD; Andréanne Marion⁶; Patrick Michel Archambault^{1,2,3}, MD, MSc, FRCPC

¹Faculty of Medicine, Université Laval, Quebec, QC, Canada

²Centre de recherche intégrée pour un système apprenant en santé et services sociaux, Centres intégrés de santé et de services sociaux de Chaudière-Appalaches, Lévis, QC, Canada

³VITAM - Centre de recherche en santé durable, Université Laval, Centre intégré universitaire de santé et de services sociaux de la Capitale-Nationale, Quebec, QC, Canada

⁴Faculty of Science and Engineering, Université Laval, Quebec, QC, Canada

⁵Research and Technology, Thales Canada, Quebec, QC, Canada

⁶Faculty of Medicine, Université de Sherbrooke, Sherbrooke, QC, Canada

Corresponding Author:

Patrick Michel Archambault, MD, MSc, FRCPC

Centre de recherche intégrée pour un système apprenant en santé et services sociaux

Centres intégrés de santé et de services sociaux de Chaudière-Appalaches

143 Rue Wolfe

Lévis, QC, G6V 3Z1

Canada

Phone: 1 418 835 7121 ext 3905

Email: patrick.archambault@fmed.ulaval.ca

Abstract

Background: Future long-duration space exploration missions, such as traveling to Mars, will create an increase in communication time delays and disruptions and remove the viability of emergency returns to Earth for timely medical treatment. Thus, higher levels of medical autonomy are necessary. Crew selection is proposed as the first line of defense to minimize medical risk for future missions; however, the second proposed line of defense is medical preparedness and crew member autonomy. In an effort to develop a decision support system, the Canadian Space Agency mandated a team of scientists from Thales Research and Technology Canada (Québec, QC) and Université Laval (Québec, QC) to create an evidence-based medical condition database linking mission-critical human conditions with key causal factors, diagnostic and treatment information, and probable outcomes.

Objective: To complement this database, we are currently conducting a scoping review to better understand the depth and breadth of evidence about managing medical conditions in space.

Methods: This scoping review will adhere to quality standards for scoping reviews, employing Levac, Colquhoun, and O'Brien's 6-stage methodology; the reported results will follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) extension for scoping reviews. In stage 1, we identified the research question in collaboration with the Canadian Space Agency (CSA), the main knowledge user. We prioritized 10 medical conditions: (1) acute coronary syndrome, (2) atrial fibrillation, (3) eye penetration, (4) herniated disk, (5) nephrolithiasis, (6) pulmonary embolism, (7) retinal detachment, (8) sepsis, (9) stroke, and (10) spaceflight associated neuro-ocular syndrome. In stage 2, with the help of an information specialist from Cochrane Canada Francophone, papers were identified through searches of the following databases: ARC, Embase, IeeeXplore, Medline Ovid, PsychINFO, and Web of Science. In stage 3, studies will be selected and assessed using a 3-step process and emerging, refined exclusion criteria. In stage 4, the data will be charted in a table based on parameters required by the CSA and developed using Google spreadsheets for shared access. In stage 5, evidence-based descriptive summaries will be produced for each condition, as well as descriptive analyses of collected data. Finally, in stage 6, the findings will be shared with the CSA to guide the completion of this project.

Results: This study was planned in December 2018. Stage 1 has been completed. The initial database search strategy with all target conditions combined identified a total of 10,403 citations to review through title and abstract screening and after duplicate removal. We plan to complete stages 2-6 by the beginning of 2021.

Conclusions: This scoping review will map the literature on the management of 10 priority medical conditions in space. It will also enable us to identify knowledge gaps that must be addressed in future research, ensuring successful and medically safe future missions as humankind embarks upon new frontiers of space exploration.

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KEYWORDS

spaceflight; astronauts; microgravity; weightlessness; acute coronary syndrome; arrhythmia; atrial fibrillation; eye penetration; intraocular foreign body; herniated disk; nephrolithiasis; pulmonary embolism; retinal detachment; sepsis; stroke; spaceflight associated neuro-ocular syndrome

Introduction

Future long-duration space missions lead to increases in communication time delays and disruption, and render emergency returns to Earth for timely medical treatment an impossibility. This is why future long-duration space travel, such as travel to Mars (whose orbital radius and period is very different from Earth's), will require higher levels of medical autonomy. To enhance space crew members' autonomy in the management of acute mission-critical events, and to minimize health issues and degradation in space, a decision-aid system must be developed to support astronauts' medical autonomy. This system would help support the management of crewmembers' health during a mission, and the planning and development of high-priority medical technologies and capabilities for extended space exploration.

Crew selection is proposed as the first line of defense to minimize medical risk for future missions; however, the second line of defense is medical preparedness and autonomy. Consequently, exploration-class missions should benefit from intelligent medical systems to support the crew in medical diagnosis, monitoring, treatment, and maintenance of clinical skills [1]. Some recent efforts along these lines include methods and algorithms for generating clinical decision rules [2,3], trend analysis for prognosis and health management [4], and work on developing data architecture for a clinical decision-support system for future exploration [5]. In an effort to develop this decision-support system, the Canadian Space Agency mandated a team of scientists from Thales Research and Technology Canada (Québec, QC) and Université Laval (Québec, QC) to create an evidence-based medical condition database linking mission-critical human conditions with key causal factors, diagnostic and treatment information (including knowledge, skills, equipment, and material needed), and probable outcomes [6]. In order to complement this database, we will conduct a scoping review to better understand the depth and breadth of evidence about managing medical conditions in space.

Our specific objectives are to (1) synthesize the current knowledge about managing medical conditions in space and (2) identify knowledge gaps to be addressed with future research and technology development to ensure better planning and

support for long-duration space exploration-class missions requiring medical autonomy.

Methods

Overview

A scoping review will be conducted to map the management of medical conditions in space, as this research area consists mostly of emerging evidence. This review will be planned and conducted in adherence to standards of quality for scoping reviews, employing the Levac 6-stage methodology [7]; the results will be reported following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) extension for scoping reviews [8].

Stage 1: Identifying the Research Question

This stage was completed during the planning of this study with the Canadian Space Agency (CSA), our main knowledge user. Results of this effort are published elsewhere [6]. In summary, our research team prioritized 10 medical conditions among the list of 100 conditions from the Integrated Medical Model Medical Conditions list [9]. This list was initially produced by National Aeronautics and Space Administration (NASA) researchers to establish which medical conditions were most relevant (eg, high likelihood of occurrence) to prepare risk mitigation for future long-duration spaceflight. Using this list, our team applied a set of criteria to help us prioritize the top 10 conditions for which the crew would need enhanced medical autonomy; these criteria were a high risk to the mission, high level of contagion, high likelihood of occurring, a critical treatment time window, different treatment in space, communication frequency, and communication bandwidth. After validating this set of criteria with the CSA, our team produced the final list of 10 target medical conditions, which will be the focus of this scoping review: (1) acute coronary syndrome, (2) atrial fibrillation, (3) eye penetration, (4) herniated disk, (4) nephrolithiasis, (5) pulmonary embolism, (6) retinal detachment, (7) sepsis, (8) stroke, and (9) spaceflight-associated neuro-ocular syndrome (SANS; formerly called visual impairment and intracranial pressure syndrome) [10].

Stage 2: Identifying Studies and Grey Literature

In collaboration with an information specialist working at Cochrane Canada Francophone, we identified the following

scientific databases to be searched: Aerospace Research Central (ARC), Embase, IeeeXplore, Medline Ovid, PsychINFO, and Web of Science. Our search strategy for each database used the following keywords: “astronaut,” “cosmonaut,” “weightlessness,” “space flight,” “spacecraft,” “long-duration space exploration missions,” “space simulation,” “aerospace,” “analog environment,” “deep space,” “ecological system,” “extraterrestrial,” “planets,” “countermeasure,” “United States National Aeronautics and Space Administration,” “aerospace medicine,” “environmental medicine,” “space medicine,” and a series of keywords targeting our 10 selected conditions. These strategies were reviewed and accepted by experts at the CSA and can be found in [Multimedia Appendix 1](#).

Study identification will be supplemented by a grey literature search using the Google search engine and by reviewing reports available through CSA and NASA websites and personal libraries. We will also review documents from included articles’ reference lists to ensure the inclusion of all relevant studies.

Stage 3: Selecting Literature

A 3-Step Evaluation Process

A 3-step process will be used to evaluate publications identified during the previous step and on emerging, refined exclusion criteria. After identifying references from our initial search strategy, we will compile references in a Google spreadsheet, with a unique identification number assigned to each article.

Step 1

First, 3 reviewer pairs will independently screen titles and abstracts based on a set of inclusion and exclusion criteria defined through team discussion. The following papers meet the selection criteria and will be retained for the second step of screening: studies about disease events in space, studies about disease events in analog environments (eg, bed rest, head-down tilt, research stations in isolated environments), studies about the incidence or prevalence of disease occurring during space travel or in astronauts (for space or the astronaut cohort from 1990 onward), studies about equipment or protocols developed for space application (from 1985 onward), and studies about diagnostic tests or devices evaluated in space. Papers will be excluded if (1) they were not written in English or French; (2) their content or topic is not relevant to space travel (eg, false keyword identification, technology or protocol only); (3) they did not address the 10 target conditions; (4) they were an editorial, letter to the editor, or abstract only, or they were strictly conceptual, a clinical image piece, or a nonscientific publication; (5) they represented a study about incidence or prevalence of diseases occurring in space or an astronaut cohort published before 1990; (6) the cohort was ill-fit (eg, young children, sick population); (7) the methods were inadequately described (validity unclear); (8) the results were invalid (fatal flaws to the methodology), or (9) the publication was a duplicate. Studies on disease incidence or prevalence occurring in space or astronaut cohorts published before 1990 will not be considered because they are most likely not representative of current epidemiologic factors and crewmembers’ health.

To ensure a consistent application of criteria and to obtain a high level of agreement, screening training sessions between at least one member of each team will be conducted for a first set of approximately 500 citations. Once inclusion and exclusion criteria for the first round are fully understood and applied uniformly between members, the remaining articles will be divided and coded by the team pairs. Each publication will be reviewed by at least 2 members of each team. All disagreements will be resolved through discussions.

Step 2

A second round of title and abstract screening will be performed by pairs of reviewers with a new set of refined selection criteria to better define the scope of manuscripts to include in stage 4, when data charting will be performed.

Step 3

After narrowing down the article list and better defining this review’s final scope for stage 4, pairs of reviewers will proceed to a third and final round of screening, using full-text when available. New, refined exclusion criteria will be determined and then applied after reading included papers from the second round. These new exclusion criteria will be used to decide if data from papers should be charted in stage 4 and included in the final results of the scoping review (stage 5).

Stage 4: Charting the Data

A data-charting table will be developed using Google spreadsheets for shared access. The table will be based on parameters required by the CSA for its medical conditions parameter database: medical condition name, medical condition category, systematized nomenclature of medicine clinical terms (SNOMED CT) identifier, definition/description of medical condition, incidence/prevalence, risk factors, level of medical knowledge, medical skills, differential diagnosis, history/symptoms, physical findings/signs, imaging, laboratory tests, physiological measurements, psychometric test, pharmacotherapy, nutritional therapy, surgical treatment, physical therapy, medical management/outcomes, support machines, instruments, and disposables. These parameters were selected and refined by reviewers.

The charting table will be trialed for the first 20 studies for refinement as part of an iterative process in which members will update the form until consensus is reached on the final version. The table contained the following parameters to describe each selected paper: a description of the study’s research question (population, intervention, comparison, outcomes, study type), the study subject (human, animal, virtual/theoretical, cadaver, cell culture, infectious pathogen), the study context (space, analog environment, Earth), incidence of disease, the prevalence of disease, the proposed physiopathology in space, risk factors, the odds ratio associated with the risk factor, medical skills for diagnosis, symptoms, physical signs/findings on physical exam, imaging, laboratory tests, physiologic measurements, clinical prediction rules, psychometric tests, pharmaceutical drug treatment, surgical treatment, other treatments (eg, physical therapy, nutritional therapy), medical skills for treatment, medical instruments and equipment, the medical management and outcome, clinical

relevance (if it's a basic science paper), and the study limitations. Definitions for each parameter will be refined by the group to ensure a common understanding and a consistent application during coding and data extraction. Individual reviewers will then extract data for all retained studies included in the third phase. A third reviewer will review discrepancies or disagreements in extraction to resolve them in a group consultation.

Stage 5: Collating, Summarizing, and Reporting Results

Collating and Summarizing

A team of reviewers will summarize the data corresponding to the parameters previously mentioned in the charting stage. This description will map out the literature on selected medical conditions in space. Our analysis will remain descriptive, as publication characteristics and, subsequently, extracted information will be heterogeneous between studies. The publication frequency for each of the 10 target conditions, the type of subjects studied (human vs animal vs theoretical model), and the study context will be reported for each study. The other parameters mentioned in stage 4 will also be presented, and evidence-based descriptive summaries for each target condition will be created. These summaries will contain qualitative and quantitative evidence extracted from selected papers in previous stages.

Reporting Results

To present our study results, we will compose a narrative description of the search decision process and a search decision flowchart. Our flowchart will detail results from the search strategy, removal of duplicate references, additions from grey literature and reference checking, and the final number of included publications per medical condition.

To present the results of our data extraction, we will employ descriptive tables and charts. Distribution of publications by medical condition in chart form will help illustrate which medical conditions lacked evidence and should be further investigated. A first table will include the list of retained publications, accompanied by a summary of relevant extracted data on parameters previously mentioned for long-duration deep space exploration. A detailed version of extracted data will be available in appendices. A second table will focus on limitations identified in included studies, either stemming from the methodology or the results. These tables will help knowledge users quickly grasp what is known about the 10 priority medical conditions in space and the current knowledge gaps that need to be addressed in future research directions.

Stage 6: Consulting Knowledge Users

Prior to conducting this study, the CSA had defined a predetermined set of important parameters for data extraction. During this last stage, we will continue sharing our findings with the CSA to guide the completion of the scoping review. Their feedback will serve as a foundation for future research directions. This stage will enable the CSA to build on the presented results and offer content expertise and perspective to our findings.

Results

This study was planned in December 2018. Stage 1 has been completed. The initial database search strategy with all target conditions combined identified a total of 10,403 citations to review through title and abstract screening and after duplicate removal. We plan to complete stages 2-6 by the beginning of 2021.

Discussion

The proposed scoping review will provide an overview of the existing literature on the management of 10 priority medical conditions in space. It will also highlight the knowledge gaps to be filled before international space agencies conduct astronomical missions to Mars. Knowledge gaps may be due to methodological flaws or limitations or simply a lack of primary studies. By identifying the gaps, we believe that it will help direct future high-quality and relevant research addressing areas in need of more primary research. Our work also seeks to synthesize the emerging evidence on 10 target medical conditions in space. We expect our scoping review to synthesize evidence about the diagnostic and therapeutic challenges facing medical crews supporting long-term space missions.

Scientific and technological progress continue to advance, making long-duration spaceflight, such as missions to and from Mars, a possibility in the foreseeable future. Developing a robust, well-equipped spacecraft is not the only requirement necessary for a successful space mission. As highlighted in a review [11] of NASA's Human Research Program's priority risks for crew health, spaceflight poses unique health and performance risks, including space radiation, SANS, and nutritional concerns that must be controlled to ensure mission success. Therefore, medical support and autonomy are crucial, as the ability to rapidly evacuate a crewmember to Earth will be impossible. However, administering medical care in space presents multiple challenges that have yet to be resolved.

Space technologies such as satellite and geographic information systems have been applied to global health on Earth [12]; however, the application of Earth-based medical technologies during long-duration space missions has not been widely documented. Extended range missions, such as a trip to Mars, have remained theoretical up to this point. Therefore, we can only hypothesize about medical needs and onboard medical and technological capabilities. This partially explains why space medicine research seems to focus more on predicting and preventing medical events [13] than treating diseases that could occur [14]. Monitoring vital signs with sensors, dosing relevant biomarkers, developing crewmembers' medical skills, and utilizing artificial intelligence and diagnostic algorithms are all strategies currently being explored by space scientists to help astronauts achieve medical autonomy during deep space missions [14].

Ultimately, we hope our work will help space agencies understand the current possibilities and limits of medical care and management of urgent medical conditions during long-duration spaceflight. This will contribute to informed

decisions about the appropriate level of medical training for crew members and the medical equipment and devices needed to ensure diagnosis and treatment in space.

This scoping review will map the literature on the management of 10 priority medical conditions in space. It will also enable us to identify knowledge gaps that must be addressed in future research, ensuring successful and medically safe future missions in humankind's pursuit of new frontiers of space exploration.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Database search strategies.

[[PDF File \(Adobe PDF File\), 120 KB - resprot_v10i3e24323_app1.pdf](#)]

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Abbreviations

CSA: Canadian Space Agency

NASA: National Aeronautics and Space Administration

SANS: spaceflight-associated neuro-ocular syndrome

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Protocol

Influence of Self-Compassion on the Health of Midwives and Nurses: Protocol for a Scoping Review

Mitra Javanmard^{1*}, BM, RM, BHSc (Hons), PhD; Mary Steen^{1*}, RN, RM, Dip ClinHypn, BHSc, PGDipHE, MCGI, PhD; Rachael Vernon^{1*}, BN, RN, MPhil (Distinction), PhD

UniSA Clinical and Health Sciences, University of South Australia, Adelaide, Australia

* all authors contributed equally

Corresponding Author:

Mitra Javanmard, BM, RM, BHSc (Hons), PhD

UniSA Clinical and Health Sciences

University of South Australia

Centenary Building, 108 North Terrace

City East Campus

Adelaide, 5000

Australia

Phone: 61 425477771

Email: mitra.javanmard@unisa.edu.au

Abstract

Background: Self-compassion is recognized to have a positive effect upon a person's health. However, the influence of self-compassion on the health of midwives and nurses is less well understood. Midwives and nurses often work in highly demanding environments and situations, and are exposed to multiple work-based stressors simultaneously. Stressors such as a demanding clinical workload, high acuity, missing breaks, working more than their contracted hours, insufficient resources and staff, and poor patient outcomes can lead to midwives and nurses feeling physically exhausted and at increased risk of poor mental health. Self-compassion may act as a protective factor, assisting midwives and nurses to remain healthy.

Objective: This scoping review will provide an overview of the evidence base relating to the influence of self-compassion on the health of midwives and nurses.

Methods: The purpose of a scoping review is to comprehensively and systematically review the literature and identify key evidence or gaps. The search strategy for this protocol includes electronic databases such as Medline, Embase, Emcare, PsycInfo, Joanna Briggs Institute, Cochrane Library, and Scopus. Grey literature sources will be also searched, including ProQuest Central, internet search engines (Google Scholar), and manually searched key journals and reference lists of relevant articles. This scoping review will be undertaken in seven stages, guided by established scoping review methods and reporting guidelines: (1) identifying the research questions; (2) identifying relevant studies; (3) selecting the studies; (4) charting the data; (5) collating, summarizing, and reporting the results; (6) consulting; and (7) dissemination of knowledge. Data will be abstracted and presented using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews checklist and explanation by three independent researchers.

Results: A preliminary search conducted in Medline (OVID) retrieved 194 results. Completion of the review is expected in December 2020 and will be published in early 2021.

Conclusions: To our knowledge, this will be the first scoping review of evidence-based literature relating to the influence of self-compassion on the health of midwives and nurses. It is anticipated that this analysis of the literature will contribute to understanding how midwives and nurses may use self-compassion in a proactive way to reduce work-based stressors such as burnout, stress, and compassion fatigue. Furthermore, the findings may inform educational needs with implications for clinical practice.

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KEYWORDS

self-compassion; self-worth; self-appreciation; self-kindness; midwives; nurses

Introduction

Background

The focus of this scoping review relates to the influence of self-compassion upon midwives and nurses, and how this concept may assist midwives and nurses to remain healthy. According to the World Health Organization (WHO) [1], health is defined as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.” Therefore, health describes more than the mere integrity of the physical body [1]. Physical health and mental health are fundamentally connected and profoundly affect each other [2]. The WHO [3] specifically defines mental health as “a state of well-being in which the individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community.” More recently, Galderisi et al [4] has related mental health to social values and roles:

mental health...enables individuals to use their abilities in harmony with universal values of society. Basic cognitive and social skills; ...flexibility and ability to cope with adverse life events and function in social roles.

Self-compassion is a concept of Buddhist philosophy in which a person has the ability to treat oneself with kindness, warmth, and acceptance in times of need [5,6]. Neff [5] and Heffernan et al [7] have described self-compassion as turning compassion inward, and being kind to yourself, and to acknowledge your own humanity, imperfection, and fragility. Neff [5] defined self-compassion as: “being touched by and open to one’s own suffering, not avoiding or disconnecting from it, generating the desire to alleviate one’s suffering and to heal oneself with kindness.”

Three interconnected components have been defined that determine self-compassionate reactions to personal negative emotions and experiences [5,8]: self-kindness versus self-judgment, sense of common humanity versus isolation, and mindfulness versus overidentification. Self-kindness describes an understanding behavior toward oneself in the face of suffering. Common humanity describes the recognition that life stresses and experiences are shared human experiences, rather than an interpretation that they are separate from those of others. Mindfulness describes the balanced awareness of negative thoughts and feelings rather than their overidentification. These individual components are assumed to interact to generate a self-compassionate frame of mind [9]. It has been reported that self-compassion and mindfulness can improve health care professionals’ mental health [10,11] by enhancing optimism [12,13], happiness [14], and by looking at problems from a larger perspective [15].

Understanding and increasing self-compassion in health care professionals continues to be an important yet underrepresented area of research. High rates of work-related stress and burnout in health care professionals [16] can lead to depression, anxiety, sleep disturbances, and fatigue [17]. It has been highlighted that when a person has the ability to have self-compassion, they are more inclined to have good interpersonal relationships and

experience a greater sense of happiness when compared to a person who has an impairment in self-compassion [18]. Adversely, a lack of self-compassion is associated with psychological distress [19].

Previous studies have suggested that the overall well-being of health care professionals has been influenced by self-compassion [20] by involving self-care behaviors such as allocating time for good nutrition [21], regular outdoor activities and exercise [20-22], and relaxation and spirituality activities [20,21,23]. Importantly, happiness levels can be improved through self-compassion and the use of adaptive behavioral and cognitive tasks [18,24].

Stressors such as a demanding clinical workload, high acuity, missing breaks, working more than their contracted hours, and insufficient resources and staff can lead to midwives and nurses feeling physically and mentally exhausted in the long term [20]. Midwives dealing with pregnant women experiencing stillbirth [25], and oncology nurses looking after patients who are in severe pain, distress, and approaching death [26] are examples of experiences that may lead to negative psychological outcomes. These factors and experiences can have a negative impact on the care given by these midwives and nurses [7].

However, it has been reported that high levels of self-compassion can positively increase overall health and psychological well-being [27-29], whereas low levels of self-compassion are associated with anxiety, stress, and depression [5]. Therefore, self-compassion may act as a protective factor, and help midwives and nurses to remain mentally and physically healthy.

Enhancing self-compassion as a focus of mindfulness education or training has been shown to increase compassionate self-care in health professionals [6,30]. Self-compassion education or training has been recommended for health professionals to help them cope with daily anxiety and stress while providing care, and increasing awareness of the benefits of self-compassion [14]. Therefore, this scoping review will search the literature investigating or exploring the influence of self-compassion for midwives and nurses. It is anticipated that the findings will inform educational needs with implications for self-compassion in clinical practice.

Aim and Objectives

The initial aim of this scoping review was to identify the influencing factors of self-compassion on midwives. After an initial search, only three studies were found that reported on the influence of self-compassion for midwives [20,31,32]. The published literature appears to have focused mostly on nurses, with a distinct global gap in evidence investigating the influence of self-compassion among midwives. Due to a lack of research studies on midwives, the aim of this scoping review was expanded to include nurses.

The aim of this review is to scope all forms of contemporary literature to determine if there is evidence of self-compassion influencing the health of midwives and nurses. The review objectives are to identify studies that have either investigated or explored factors that influence midwives’ and nurses’ self-compassion, and map factors that positively or negatively

impact their health. The review will also identify studies that have directly evaluated education or training programs that focus on self-compassion for midwives and nurses.

Methods

Scoping Review

A scoping review was considered the most appropriate design to address the objectives of this review for several reasons. First, the aim and objectives of this review are broad, and unlike a systematic review or meta-analysis, this scoping review is not trying to answer a specific question but rather to “examine the extent, range, and nature of a research activity” [33]. Second, a scoping review is rigorous, and requires implementation of a comprehensive and systematic approach to searching for relevant literature. Undertaking a scoping review is considered the most appropriate approach to gather evidence from studies using a variety of methodologies, or where there are no reviews being undertaken on the specific topic [34].

This scoping review will primarily use the method established by Arksey and O’Malley [35], incorporating improvements suggested by Levac et al [33] and Peters et al [36], and the adjustments made by Tricco et al [37]. Methodological stages include (1) identifying the research question; (2) identifying relevant studies; (3) selecting studies; (4) charting the data; and (5) collating, summarizing, and reporting the results. Adding two stages, (6) consultation and (7) disseminating the knowledge [33,37], will assist in contextualizing all of the methodological stages utilized to undertake this review. Reporting will be conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines [37]. The population, concept, and context (PCC) mnemonic will be used to develop the research questions and search strategy for this scoping review [37].

Stage 1: Identifying the Research Questions

Population

All qualified and registered midwives and nurses who are practicing midwifery and nursing (full time, part time, and casual) will be included in the scoping review. Midwives and nurses in an academic position or undertaking research are also included. Midwives and nurses with dual registration are included. Nursing assistants and supporter workers are not included. Midwifery and nursing students are also excluded. To clarify, a midwife is recognized as

a responsible and accountable professional who works in partnership with women to give the necessary support, care and advice during pregnancy, labour and the postpartum period, to conduct births on the midwife’s own responsibility and to provide care for the newborn and the infant [38]

A nurse is defined as “a person who has completed a program of basic, generalized nursing education and is authorized by the appropriate regulatory authority to practice nursing in his/her country” [39].

Concept

Self-compassion, generally defined as being kind to yourself, focusing on midwives and nurses and how self-compassion may be a buffer and offer some protective mechanism to remain healthy will be reviewed. The concept of self-compassion comprises six components: self-kindness versus self-judgment, common humanity versus isolation, and mindfulness versus overidentification. The influencing factors of these components upon midwives and nurses will be reviewed. The focus of this scoping review is specifically related to self-compassion and its components; therefore, other subject headings such as self-care, self-efficacy, or empathy will not be reviewed.

Context

The scoping review will consider studies that involved qualified and registered midwives and nurses undertaken in any health care setting, including, but not restricted to, hospitals and community, medical, and educational centers. Research involving self-compassion education for midwives and nurses will be reviewed. The original Self-Compassion Scale (SCS) is a 26-item questionnaire and widely used self-report measure developed to assess the six components of self-compassion [40]. Furthermore, a shorter version (12 items) of the SCS has been developed [41]. Therefore, studies that have utilized validated measures for self-compassion will be included. The effectiveness of self-compassion measurement scales, and education or training provided for qualified midwives and nurses will be reported.

Formulating the Final Research Questions

According to Arksey and O’Malley [35], this scoping review will follow an iterative process for developing the research questions. Initially, broad research questions were conceived to ensure that the review will identify the diversity and scope of the literature available. However, as this review continues, the research questions may be reformulated and new questions may appear over time. The final questions are: (1) Is there evidence of specific factors associated with self-compassion upon midwives’ and nurses’ health status? (2) How have the included studies reported on the measurement and effectiveness of self-compassion? (3) Is there evidence to support self-compassion education or training for midwives and nurses, and is this associated with improved health outcomes? (5) Have studies reported any challenges or limitations upon implementation of self-compassion education or training for midwives and nurses?

The aim of this scoping review will comprehensively address these broad research questions; however, key elements will conceptualize the review aim and objectives to guide the search strategy.

Stage 2: Identifying Relevant Studies

Types of Studies

This review will consider all types of studies, including quantitative, qualitative, and mixed-methods studies. All types of quantitative studies will be included (eg, cross-sectional studies, correlational studies, randomized controlled trials [RCTs], non-RCTs, single-case studies, and case-control

studies). Furthermore, all types of qualitative studies will be included (eg, ethnography, phenomenology, grounded theory) and mixed methods (eg, convergent, exploratory, and explanatory sequential and advanced designs). Other types of studies such as systematic reviews and scoping reviews will also be considered. To be included in the review, studies will need to consider at least one component of self-compassion measured with a self-compassion scale among midwives and nurses.

Self-compassion scales utilized in reviews and conference abstracts will be reviewed and reported separately in the Discussion section. Only results and findings of primary studies will be reported in the Results section. Letters to the editor, commentaries, case reports, and ongoing studies are also excluded. The review is limited to papers written in English. Due to the increasing focus on self-compassion in the last two decades in western society, this scoping review will include relevant studies published from 2000 to 2020.

Databases

Specific keywords and controlled vocabulary terms will be used to maximize sensitivity and specificity within the search. The

search strategy will aim to find both published and unpublished English-language studies. The search strategy was developed in Medline via the Ovid platform. The details of the search in Medline are presented in [Multimedia Appendix 1](#). The search will be expanded to include the Embase, Emtree, PsycInfo, Joanna Briggs Institute (Ovid), Scopus, and Cochrane Library (Wiley) databases to identify articles on this topic, followed by analysis of the text words contained in titles and abstracts, and index terms used to describe these articles. The following database sources will be searched to identify any grey literature: ProQuest Central and Google/Google Scholar, and the bibliographies of relevant studies and reviews. Additionally, the reference lists of eligible studies will be sourced. This approach will inform the development of a search strategy, including identified keywords and index terms that will be adapted for each information source. As the focus of this scoping review is on self-compassion, MeSH (Medical Subject Heading) terms such as self-care, self-efficacy, or empathy will not be reviewed. A search strategy is provided in [Table 1](#).

Table 1. Draft search terms.

Category	Search terms
Participants	Midwives OR midwi* OR nurses OR nurs*
Concept	Self-compassion* OR Self?compassion OR Self-kindness* OR self?kindness OR Self-worth* OR self?worth OR Self-appreciation* OR self?appreciation
Context	Health care facilities (eg, community and medical centers and hospitals) Educational centers (eg, universities)
Study types	Quantitative, qualitative, and mixed-methods research studies

The complete and final search strategy will be provided in a follow-up publication. Searches will also be rerun prior to the final analyses to retrieve any subsequent studies that meet the inclusion criteria. If additional sources are identified while the review is being performed, the inclusion of these sources will be documented. Upon completion, the results from each database will also be documented.

Stage 3: Study Selection

All references from the initial main search will be exported to Covidence (a web-based source selection tool) for eliminating duplicates, screening of titles and abstracts, and full-text reviews. After excluding duplicates, two reviewers will screen the title and abstract for each of the papers according to the proposed eligibility criteria. To refine the web-based source selection tool, pilot testing of a random sample of 25 titles/abstracts will be undertaken by the authors. Any discrepancies will be discussed and modifications will be made [42]. The full-text version of potential suitable papers will then be read and screened by two reviewers against the inclusion/exclusion criteria. A separate appendix will be submitted for excluded sources and the reasons for exclusion will be stated using Covidence [41]. Consensus will be reached by agreement.

If there are any cases of disagreement between the two reviewers, which cannot be resolved through discussion, a third independent reviewer will be asked to assess the paper(s) in question and consensus will be reached by agreement. The selection process will be reported using a PRISMA-ScR flow diagram [37].

Stage 4: Charting the Data

Data charting will be used for extracting data from included studies in scoping reviews [33,35,36]. A standardized data extraction spreadsheet template will be developed using Microsoft Excel to extract data from all papers meeting the inclusion criteria. Data will be charted by one reviewer and checked by another reviewer. Any discrepancies will be resolved by consensus of the research team. Pilot testing of 5-10 full-text articles for data charting will be undertaken to ensure that key information is extracted completely [42]. Data extraction will be an iterative process, incorporating an initial trial of data charting and team consultation throughout the process to ensure consistency with the review purpose and questions, and to include new questions that may arise during the process. Regular communication between reviewers will facilitate this process and ensure the reliability of data charting. This approach will

be based on providing the data necessary for addressing the main objective of this review; that is, to identify factors that influence midwives' and nurses' self-compassion, and map factors that positively or negatively impact their health. At present, these categories include (but are not limited to): bibliographic information of the study, study aims, research design, setting/context, number of participants, measure(s) used to assess the influential factors of self-compassion,

self-compassion education or training (if applicable), analyses conducted, results of statistical analyses, and summary of findings. Furthermore, the authors of this scoping review will provide their own interpretations regarding conclusions, strengths, limitations, and recommendations of included studies. A draft of the data extraction tool is presented in Table 2. This draft will be modified and revised as necessary during the process of extracting data from each included study.

Table 2. Relevant studies.

Data	Details to be extracted (if available)
Publication summary	Author(s), year, location, title, aim(s), type of study
Settings	Hospital, university, etc
Population	Total sample size
Self-compassion scales	The Neff Self-Compassion Scales 24-item; Short Version SCS 12-item
Other used scales (if applicable)	Copenhagen Burnout Inventory 19-item to measure burnout; Perceived Stress Scale 10-item to measure stress; Professional Quality of Life Scale, version 5 to measure compassion satisfaction
Factors associated with self-compassion	Burnout, stress, and compassion satisfaction, etc
Self-compassion education or training (if applicable)	Any used scales
Outcomes	Any identified factors affected by self-compassion
Others	Conclusions, strengths and limitations, recommendations

Stage 5: Collating, Summarizing, and Reporting the Results

The purpose of this scoping review is to collate research findings and present an overview of all material reviewed, rather than a systematic synthesis of evidence that provides results on a narrowly defined question. Stage 5 of the review will be completed in three steps: analyzing (collating and summarizing) the data, reporting results, and applying meaning to the results.

The first step will involve analyzing quantitative data, and the results of individual studies will be analyzed and tabulated. Any qualitative data will be analyzed thematically and reported either narratively or tabulated. Additionally, further narrative description of all results will be provided to aid interpretation of the findings as they relate to the research questions. The tables will report on distribution of studies by type, year of publication, country of origin, research methods, all utilized scales, factors associated with self-compassion, and findings.

For reporting results, a narrative summary, represented by categories, will describe how the results relate to the review aim and objectives. The results will be classified in main conceptual categories that will be obtained during the results extraction. Specific factors that influenced completeness and usefulness will be grouped by domain, and the final list of factors will be determined and agreed on by all reviewers. The final synthesis of the reviewed literature will be presented in tables, graphs, or charts, complemented by a narrative description.

The final step will apply meaning to the results, and a narrative descriptive approach will be used to highlight gaps in existing research evidence, and consider the implications of findings within the broader context such as research, policy, and practice.

Stage 6: Consulting

The consultation stage will be used to add methodological rigor, and to ensure applicability and usability of the results [33]. To reach this goal, the reviewers will share preliminary findings from stage 5 (collating, summarizing, and reporting results) with an independent self-compassion researcher/author and a midwife or a nurse to validate the findings. The feedback will be taken into consideration and integrated within the overall review findings.

Stage 7: Disseminating the Knowledge

According to the framework suggested by Levac et al [33] and Tricco et al [37], we consider it important to make the content of this scoping review available to key stakeholders (ie, midwives and nurses), with the goal of increasing awareness of the findings and facilitate evidence-informed decision making. Following the scoping review, the reviewers will disseminate the findings several ways by authoring a journal publication, an editorial conference presentation, and a written summary report for professional midwifery and nursing organizations and social media outlets.

Results

A preliminary search performed in Medline retrieved 194 results. It is anticipated that all stages of the review will be completed in December 2020 and results will be disseminated through peer-review publications in early 2021.

Discussion

In the general population, self-compassion is associated with positive health outcomes. However, the influence of

self-compassion on midwives' and nurses' health is less well known. Midwives and nurses are often exposed to multiple work-based stressors; thus, the influence of self-compassion on their health may be an important factor that has implications for future practice. This review will provide an evidence-based overview of the influence or potential influence of self-compassion on midwives' and nurses' health. The findings of this scoping review will identify gaps in the current literature on self-compassion research, and highlight related priorities for future research for midwives and nurses. The findings may have

practical implications by identifying specific self-compassion components that can be implemented in future self-compassion education or training. One of the strengths of the proposed review is to identify if self-compassion education or training programs can potentially improve the awareness and ability of midwives and nurses to have self-compassion. We anticipate that the outcomes of this review will be relevant to midwives, nurses, researchers, clinical management, stakeholders, and commissioners on an international scale.

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Authors' Contributions

MS, RV, and MJ conceptualized the scoping review protocol. MJ and MS developed the search strategy. MJ and MS wrote the draft manuscript of the scoping review protocol with appraisal, review, and editing completed by RV. All authors have read and approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Search strategy for MEDLINE (2000 to present).

[PNG File, 75 KB - [resprot_v10i3e21917_app1.png](#)]

Multimedia Appendix 2

External peer-review report.

[DOCX File, 20 KB - [resprot_v10i3e21917_app2.docx](#)]

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Abbreviations

PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

RCT: randomized controlled trial

SCS: Self-Compassion Scale

WHO: World Health Organization

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Protocol

Mapping Evidence of Neonatal Resuscitation Training on the Practices of Unskilled Birth Attendants in Low-Resource Countries: Protocol for a Scoping Review

Adenike Adebola Olaniyi¹, BSc, MPH, PhD; Busisiwe Purity Ncama¹, BSc, MSc, PhD; Hafaza Amod¹, BSc, MSc
School of Nursing and Public Health, College of Health Sciences, University of Kwazulu-Natal, Durban, South Africa

Corresponding Author:

Adenike Adebola Olaniyi, BSc, MPH, PhD
School of Nursing and Public Health
College of Health Sciences
University of Kwazulu-Natal
238 Mazisi Kunene Rd
Durban
South Africa
Phone: 27 633580128
Email: nikyniyi2007@yahoo.com

Abstract

Background: Competence in neonatal resuscitation of the newborn is very critical to ensure the safety and well-being of newborn infants. The acquisition of neonatal resuscitation skills by birth attendants improves self-efficacy, thereby reducing neonatal mortality as a result of asphyxia. Approximately one-quarter of all neonatal deaths globally are caused by birth asphyxia. The need for neonatal resuscitation is most imperative in resource-constrained settings, where access to intrapartum obstetric care is inadequate.

Objective: This protocol describes the methodology of a scoping review on evidence of training in neonatal resuscitation and its association with practice in low-resource countries. The aim of the review is to map the available evidence of neonatal resuscitation training on the practices of unskilled birth attendants.

Methods: The scoping review will use the Population, Concept, and Context (PCC) framework proposed by Arksey and O'Malley, refined by Levac et al, and published by Joanna Briggs Institute, while following the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines. The search strategy was developed with the assistance of the college librarian. A number of databases of peer-reviewed research (PsycINFO and Wiley Online Library [via EBSCOhost], PubMed, MEDLINE with full text, Google Scholar [via ScienceDirect], and CINAHL Plus with full text [via EBSCOhost]) and databases committed to grey literature sources will be searched, and reference extraction will be performed. Two independent reviewers will screen and extract data, and discrepancies will be resolved by a third reviewer. The extracted data will undergo a descriptive analysis of contextual data and a quantitative analysis using appropriate statistical methods.

Results: Data relating to neonatal resuscitation training and practices in low-resource settings will be extracted and included for analysis. We expect that the review will be completed 12 months from the publication of this protocol.

Conclusions: This scoping review will focus on the review of evidence and provide an insight into the existing literature to guide further research and identify implementation strategies to improve the practices of unskilled birth attendants through the acquisition of skills and self-efficacy in neonatal resuscitation. The results of this review will be presented at relevant conferences related to newborn and child health and neonatal nursing studies and published in a peer-reviewed journal.

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KEYWORDS

neonatal resuscitation; newborn; neonatal; low- and middle-resource countries; training; birth; infant; baby; obstetrics; protocol; review

Introduction

Annually, an estimated 10 million babies need help to initiate breathing, although all babies require an immediate assessment at birth [1]. Approximately, 5% to 10% of all babies born in health facilities need some measure of resuscitation, including tactile stimulation, airway clearance, and positioning [2]. According to the report of the World Health Organization (WHO), approximately 3% to 6% of neonates require basic neonatal resuscitation, which consists of simple initial steps as well as assisted ventilation [3]. Neonatal resuscitation refers to a set of interventions performed at the time of birth to support the establishment of breathing and circulation in newborns [4]. Most babies with primary apnea respond to stimulation, including drying and tactile stimulation, and will not require ventilation. Performing basic resuscitation with bag and mask is required for babies who cannot breathe and sufficient to resuscitate neonates with secondary apnea [4]. Advanced resuscitation (performed by skilled birth attendants), which comprises chest compressions, intubation, or medication, is essential for approximately 2% of all nonbreathing babies [5].

Identification of birth asphyxia in a newborn and prompt resuscitation requires immediate availability of a qualified individual, the appropriate equipment, and well-prepared action. Countries that wish to strengthen newborn resuscitation need to follow the suggested steps. In most low- and middle-income countries, birth attendants deliver more than 20 women a year. Therefore, in practice, health care institutions should introduce basic newborn resuscitation [3]. The call for neonatal resuscitation is most significant in low-resource settings, where access to intrapartum obstetric care is poor and the prevalence, mortality, and burden of long-time impairment from intrapartum-related events is highest. Delays in helping a nonbreathing neonate to establish ventilation, which occurs often in low-resource settings, may aggravate hypoxia and increase the need for assisted ventilation, thereby contributing to neonatal morbidity and mortality [1]. The impact of training birth attendants in neonatal resuscitation on mortality is restricted by the reduction of skills and knowledge over time and conveyance of skills into clinical practice [6]. Reducing neonatal death has been a rising challenge in low- and middle-resource countries in the past decade [7]. The development of low-cost interventions and their efficient delivery are desirable to reduce death from birth asphyxia. Increased mortality rates are somewhat ascribed to the shortage of trained birth attendants and a scarcity of resources [8]. Empowering unskilled birth attendants with adequate knowledge and skills in neonatal resuscitation can serve as an instrument of change for reducing newborn deaths [9]. The scoping review represents a suitable methodology for reviewing a large amount of research in order to generate an overview of the research undertaken on a topic and determine the range of studies that are available, summarize research results, and identify any evidence gaps [10]. In this context, our aim is to conduct a scoping review to examine the existing literature pertaining to the influence of training on practice. The review also seeks to map out available evidence of neonatal resuscitation training

of unskilled birth attendants, examine the existing literature pertaining to practice among unskilled birth attendants, and identify gaps in the literature regarding future research surrounding neonatal resuscitation training on unskilled birth attendants' practice where resources are limited.

Methods

Study Design

A scoping review will be conducted to identify and examine the existing research centered on the effects of neonatal resuscitation training on the practices of unskilled birth attendants in low-resource countries. In contrast to systematic reviews that aim to answer specific questions, scoping reviews produce a broad overview of the field. Hence, our study will be conducted using a methodological framework for scoping studies published by Arksey and O'Malley [8], which has been further developed by Levac et al [11] and the Joanna Briggs Institute [12]. As recommended by Tricco et al [13], this protocol will follow the relevant aspects of the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines to ensure rigor and reduce bias in reporting the methodology [14]. Using this established protocol, we plan to review the existing literature systematically focusing on neonatal resuscitation training of unskilled birth attendants on practice and map out key concepts, thereby identifying the need for further research in this area. The framework includes the following stages: (1) identify the research question; (2) identify relevant studies; (3) perform study selection; (4) extract and chart the data; and (5) collate, summarize, and report the results.

Stage 1: Identify the Research Question

The aim of this review is to identify what gaps exist within the research of neonatal resuscitation training of unskilled birth attendants and identify interventions that can be made to improve such gaps.

Furthermore, this study endeavors to create an understanding of how neonatal resuscitation training influences the practices of newborn care and what factors are essential in their implementation for achievement in a low-resource setting. We aim to provide answers to the following subquestions:

- What evidence is there that neonatal resuscitation training of unskilled birth attendants leads to competence in practice?
- What evidence is there that effective training improves newborn survival?
- What are the barriers and enablers to the efficient implementation of neonatal resuscitation?

This review will use the Population, Concept, and Context (PCC) framework (Table 1) recommended by Joanna Briggs Institute for scoping reviews [12] to determine the eligibility of the research questions. PCC is a more adaptable substitute for the Population, Intervention, Comparison, and Outcomes (PICO) framework for systematic reviews.

Table 1. Population, Concept, and Context framework for determination of the eligibility of the research questions for the review.

Criteria	Determinants
Population	The population for this review will be health care professionals who are unskilled. Skilled birth attendants—nurses, midwives, and doctors—are excluded from the review.
Concept/intervention	Neonatal resuscitation training
Context	While the literature citations for unskilled birth attendants in the African community are limited, we propose to extend the scope of this review to include low- and middle-resource countries and developing countries to increase the pool of studies included in this scoping review.

Stage 2: Identify Relevant Studies

The research team developed a search strategy with the college librarian. Our literature search was open, including peer-reviewed literature and grey literature (ie, research not published in peer-reviewed journals). Using databases of peer-reviewed research (PsycINFO and Wiley Online Library [via EBSCOhost], PubMed, MEDLINE with full-text, Google Scholar [via ScienceDirect], and CINAHL Plus with full text [via EBSCOhost]), as well as the websites of the WHO and other organizations with policies and guidelines on neonatal resuscitation, a systematic search for relevant studies was conducted. The search was limited to articles published between January 2008 and January 2019, given that we wanted to examine the effects of neonatal resuscitation training on the practices of unskilled birth attendants over an 11-year period. We also performed a nonsystematic search (or grey literature search) of reports and guidelines from agencies (eg, WHO), using search engines designed to find evidence from published relevant interventions and studies in low- and middle-income

countries, and selected grey literature reports from governmental and nongovernmental organizations.

The primary research teams were focused on using variations of the following Medical Subject Headings (MeSH) terms: resuscitation, practice, unskilled birth attendants, neonate/newborn, community health workers, training, and low/middle resource setting. In addition, a number of terms and keywords were searched, including “unskilled birth attendants,” neonatal resuscitation training, community health workers, low/middle resources setting, and unskilled birth attendants, along with the relevant subheadings. They were systematically combined into phrases using Boolean operators (AND, OR) to capture relevant fields. A complete list of the search terms is presented in [Table 2](#). All researchers will update the number of publications identified and date of each literature search using [Table 2](#). After searching, duplicates will be deleted, and the remaining papers will be exported to a web-based software platform that streamlines the inclusion eligibility screening for systematic reviews [15].

Table 2. Electronic search record.

Date searched	Keywords used ^a	Search engine or database used (number of publications)
12/4/2018	Neonatal resuscitation AND training AND practice AND community health workers AND birth asphyxia	EBSCOhost (9701); MEDLINE (543); PsycINFO (102)
15/4/2018	Neonatal resuscitation AND unskilled birth attendants AND low-resource setting	EBSCOhost (12,943); CINAHL Plus with Full Text (260); Education Resources Information Center (ERIC) (24)
17/4/2018	Neonatal resuscitation AND practice AND managing birth asphyxia in the community	Google Scholar (16,900)
20/4/2018	(“neonatal resuscitation” [MeSH terms] OR “neonatal resuscitation” [all fields]) AND “training” (MeSH terms) OR “community health workers” (all fields) OR “health workers” (all fields) AND “practice” (all fields)	PubMed (231); MEDLINE (876)
10/7/2018	Neonatal resuscitation AND practice of birth attendants AND perinatal birth asphyxia	EBSCOhost (46); Health Source: Nursing/Academic (5); Academic Search Complete (17)
12/1/2019	Neonatal resuscitation AND unskilled birth attendants	World Health Organization (41)

^a“neonatal resuscitation” OR “newborn resuscitation training” OR “perinatal birth asphyxia” OR “birth asphyxia” OR “unskilled birth attendants” OR “community health workers” OR “managing birth asphyxia in the community” OR “practice” OR “low-resource setting.”

Stage 3: Perform Study Selection

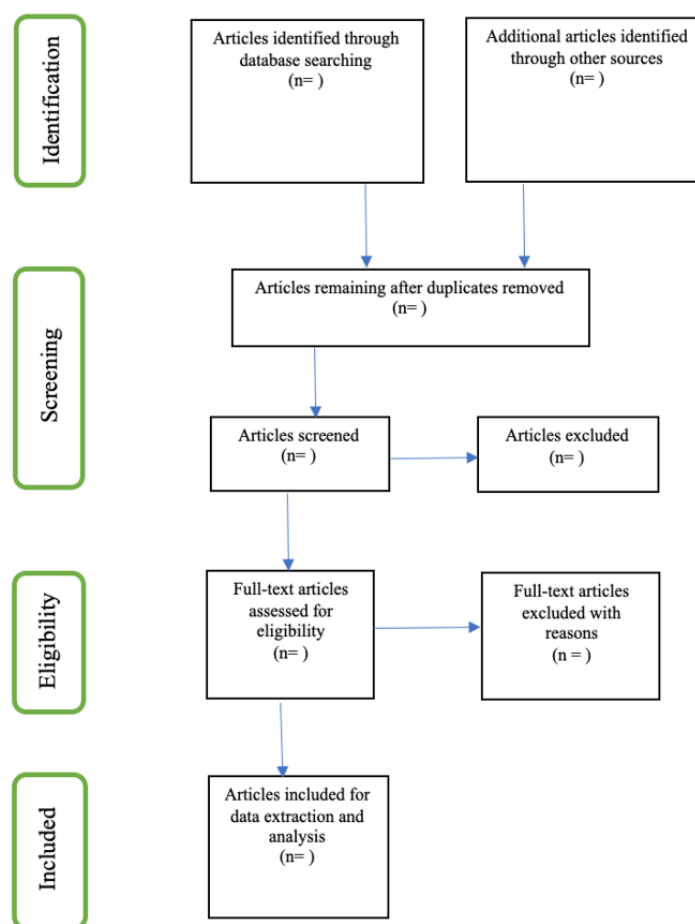
A library will be created for this review using EndNote X7.8 (Clarivate) referencing software. The investigators will search systematically and screen study titles from the database. All eligible study titles will be exported to the EndNote library. All duplicates will be removed, and abstract screening will be performed. Two reviewers (AAO and HA) will independently

conduct abstract screening, followed by full-text screening of all studies selected using guidelines from the eligibility criteria. A third reviewer (BPN) will be consulted in cases of disagreement between the reviewers.

Where articles are not available, authors will be contacted. We will exploit our local library services (University of KwaZulu-Natal) to retrieve articles to be included in the full article screening. Reporting will be done according to the

PRISMA-ScR flow diagram [14] in Figure 1. Additional articles will be identified through reference mining of included studies. Subsequently, discussion will follow to establish a consensus on which papers will be included.

Figure 1. PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) flow diagram showing the phases of the literature search for extraction and selection of studies for the review [14].



The inclusion criteria are as follows: (1) studies focused on neonatal resuscitation with unskilled birth attendants; (2) original research or reviews published in peer-reviewed journals relevant to the study; and (3) studies conducted in low- and middle-resource countries. Non-English-language studies will be excluded from the review. We will also exclude any studies without a focus on neonates or newborns and/or studies reporting preterm deaths.

Stage 4: Extract and Chart the Data

Three independent team reviewers (AAO, HA, and BPN) will extract data from all eligible studies in triplicate using a standardized Google Forms tool for the abstracts. A data charting table will be used to extract and process the information from all studies. Data to be extracted and described will include the following: bibliographic details, study design, assessment of knowledge of health providers, practices, the effectiveness of training intervention, and study setting. Information specific to community health workers as unskilled birth attendants, descriptions of interventions as neonatal resuscitation training, and geographical locations of the studies will also be extracted. The team will autonomously design and compare the form for accuracy using the PCC framework of the review for the abstract [12]. Two reviewers (AAO and HA) will independently screen and select all references and process the relevant information

from each included article. The third reviewer (BPN) will be consulted during the review to achieve harmony.

Stage 5: Collate, Summarize, and Report the Results

The main aim of this study is to scope the existing evidence and summarize the findings as presented across articles. After data extraction is concluded, the research team will carry out a thematic analysis of the studies, where a narrative account of the data extracted from the included studies will be analyzed and an overview of the reviewed data will be provided. Data will be extracted and described according to the following features: bibliographic details, study design, assessment of knowledge of health providers, practices, effectiveness of training intervention, and study setting. Emerging themes from study results on neonatal resuscitation training for birth attendants who are unskilled will be coded by all authors independently. NVivo software (version 12; QSR International Pty Ltd [16]) will be expended to code the data from the included studies according to the above classifications. More importantly, the study team will scrutinize the meaning of findings as they relate to the overall aim of the study and discuss the implications for future research, practice, and policy.

Results

We expect that the review will be completed 12 months from the publication of this protocol. The results will be reported based on the identified outcomes as specified above.

Discussion

Principal Findings

Basic neonatal resuscitation training can be successfully accomplished by health workers, resulting in a decline in intrapartum-related mortality [17]. Training programs in neonatal resuscitation can effectively increase the competence of health workers in conducting neonatal resuscitation and reduce potentially harmful practices [18]. Targeted research on neonatal resuscitation and its impact on the practice of community health workers who are unskilled birth attendants is needed. Training of community health care workers in neonatal resuscitation will enhance their skills and practice and improve the prevention of intrapartum-related deaths. Evidence from countries like India and Indonesia showed that community-based neonatal resuscitation training may be possible and helpful in reducing intrapartum-related mortality in settings with high rates of home births and delivery attendance by community health workers [19].

The proposed scoping review will generate findings that will aid in describing the links between neonatal resuscitation training and practices among community health workers who

are unskilled birth attendants. This review will enable the authors to answer key questions, clarifying what is known and unknown about the links between this phenomenon in low- and middle-resource countries.

As such, the findings of this review will contribute to knowledge on this topic and impact skills for practice, policy, and research in the area of newborn survival and child health. Evidence generated in this scoping review may serve as a basis on which prevention strategies may be established for newborn mortality as a result of perinatal asphyxia.

Furthermore, this review will be significant in identifying research gaps and other ways in which reduction in newborn mortality can be achieved. Findings in this review will become relevant to researchers as evidence for the need for more work in this area.

Strengths and Limitations of the Study

The protocol outlines a rigorous design that comprises an established research framework, a search strategy, and a selection process. The inclusion of grey literature and the use of peer-reviewed literature take into consideration a wide synopsis of various study designs and methodologies and emphasize the state of existing literature surrounding neonatal resuscitation training. The scoping review is an effective method for investigating and mapping comprehensive and different topics. The possible limitation regarding the amount of data for this scoping review study is that this study is not going to analyze the direct impact of training on mortality.

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All data generated or analyzed during the review study will be included in the published scoping review article.

Authors' Contributions

AAO and BPN conceptualized and designed the study. AAO was responsible for data collection and prepared the manuscript under the supervision of BPN and HA, who both reviewed the manuscript. AAO and HA contributed to the development of the background and planned output, methods of review, and synthesis of data. Both AAO and BPN contributed to the reviewed draft version of the manuscript and approved the final version.

Conflicts of Interest

None declared.

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Abbreviations

MeSH: Medical Subject Headings

PCC: Population, Concept, and Context

PICO: Population, Intervention, Comparison, and Outcomes

PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

WHO: World Health Organization

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