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Protocol

Providing Unique Support for Health Study Among Young Black and Latinx Men Who Have Sex With Men and Young Black and Latinx Transgender Women Living in 3 Urban Cities in the United States: Protocol for a Coach-Based Mobile-Enhanced Randomized Control Trial

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Abstract

Background: The US National HIV/AIDS Strategy 2020 calls for increasing access to care, improving outcomes of people living with HIV, and targeting biomedical prevention efforts, including access to pre-exposure prophylaxis (PrEP) in communities where HIV is most heavily concentrated. The cities of Baltimore, Maryland (MD); Washington, DC; and Philadelphia, Pennsylvania (PA) are disproportionately burdened by high rates of new cases of HIV infection, with high prevalence among young Black and Latinx men who have sex with men (YBLMSM) and young Black and Latinx transgender women (YBLTW) aged 15-24 years.

Objective: This study aims (1) to identify and recruit YBLMSM and YBLTW who are at risk or living with HIV in Baltimore, MD; Philadelphia, PA; and Washington, DC, using respondent-driven sampling (RDS) with targeted seed selection, and (2) to assess the efficacy of a coach-based mobile-enhanced intervention (MEI) compared with standard of care (SOC) to increase successful engagement and retention into HIV, PrEP, and substance use treatment care across the HIV care and prevention continua in 3 Mid-Atlantic cities. This paper describes the protocol and progress as of October 20, 2019.

Methods: This study uses a multiphase mixed methods design. The first phase is a formative, qualitative research with focus group discussions and key informant interviews. The second phase consists of evaluating the ability of RDS with targeted seed selection. The third phase includes 2 embedded randomized controlled trials (RCTs), where participants complete a baseline sociobehavioral survey, rapid HIV testing, and eligible youth enroll in parallel status-dependent RCTs that randomize the participant to 1 of 2 study arms: MEI with coach or SOC. Participants are asked to complete a web-based survey and provide biologic specimens—HIV-1 RNA (viral load) or HIV-1 antibody test and urine drug screen—at baseline and at 3, 6, and 12 months, and an exit interview at 18 months.

Results: A formative qualitative research was conducted in February 2017 and May 2018, and this led to further refinement of recruitment and study methods. Aim 1 recruitment began in September 2017 with subsequent enrollment into the RCTs. Recruitment is ongoing with 520 participants screened and 402 (77.3%) enrolled in aim 1 by October 2020. Of these, 159 are enrolled in the 2 randomized trials: 36 (22.6%) HIV-positive not virally suppressed (aim 2) and 123 (77.4%) high-risk HIV-negative (aim 3).

Conclusions: This study has the potential to significantly impact the medical and substance use services provided to YBLMSM and YBLTW in the United States by providing rigorous scientific evidence outlining approaches and strategies that improve the uptake and engagement of YBLMSM and YBLTW in the HIV treatment and prevention continuum.

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KEYWORDS

African-American; Latinx; men and transgender; HIV; youth; mobile phone

Introduction

Background

The US National HIV/AIDS Strategy 2020 [1] calls for (1) increasing access to care and improving outcomes of people living with HIV and (2) targeting biomedical prevention efforts, including access to pre-exposure prophylaxis (PrEP) in communities where HIV is most heavily concentrated. The cities of Baltimore, Maryland; Washington, DC; and Philadelphia, Pennsylvania, are disproportionately burdened by high rates of new cases of HIV infection, with highly elevated rates among young Black and Latinx men who have sex with men (YBLMSM) and young Black and Latinx transgender women (YBLTW) aged 15-24 years [2-5]. This underscores the need for increased identification, linkage, and initiation in HIV treatment and preventive care for these populations.

Strategies to change the trajectory of the epidemic for those most affected now focus on status-based cascade approaches that seek to systematically connect individuals at different stages within the HIV continuum to different stages of prevention and treatment to reduce their likelihood of acquiring HIV, and for those with HIV, achieving viral suppression [6-8]. The cascade approach seeks to identify one's HIV infection status and immediately engage the individual in HIV prevention, typically using PrEP, or in HIV care. Although earlier engagement in the HIV care cascade can improve the overall outcomes, YBLMSM and YBLTW disproportionately fall out of the treatment cascade at an early stage [9]. Both YBLMSM and YBLTW are less likely than White young men who have sex with men (MSM) or their White cisgender peers to receive, adhere, and obtain HIV viral suppression with antiretroviral therapy (ART) [10,11]. Moreover, YBLMSM and YBLTW at risk for HIV have had disproportionately lower rates of PrEP uptake and adherence [3,12,13].

High rates of substance use [14] in YBLMSM and YBLTW have been identified as key factors that influence treatment and prevention engagement [15-17]. YBLMSM and YBLTW with substance use disorders (SUDs) and *risky* substance use may be less likely to perceive a need for treatment and more likely to experience barriers to engaging in care [18,19]. Findings in other research indicate that behavioral interventions should assess substance use to inform clinical guidance in education and medical consultation for young MSM [20]. Related anxiety and other mental health diagnoses, which are often associated with substance use, may also be relevant to informing an intervention to reduce risk behavior [21]. As such, substance use interventions may increase the effectiveness of HIV treatment and prevention programs [22].

Communities of color and low-income communities often experience limited access to HIV care, substance treatment, and lesbian, gay, bisexual, transgender, queer (LGBTQ) services [19,23-26]. Multiple barriers have been identified, including barriers related to race, sexual identity, gender identity, and intersectional discrimination or stigma experienced from existing within multiple marginalized identities [27-30]. Concerns about confidentiality and mistrust have also been identified as barriers for youth [31]. Youth-based interventions that are accessible and simultaneously address HIV care, prevention, and substance use treatment behaviors are needed, yet few exist [14].

One strategy that has shown promise in identifying hard-to-reach MSM and transgender women (TW) at risk of HIV and providing them with the opportunity to receive PrEP, early ART, and substance use is a peer-driven recruitment [32]. Peer-driven recruitment has been identified as an effective strategy to reach MSM, including young Black MSM, and TW at high risk of HIV in the United States and Thailand [33,34]. In both studies, peer recruitment resulted in earlier access to HIV and prevention services, including PrEP and early ART [32,34]. Respondent-driven sampling (RDS) is a peer recruitment strategy that has been used to identify and engage hard-to-reach HIV-infected but untreated Black MSM in HIV care [32,35,36]. Typically, RDS involves a chain-referral procedure in which well-networked individuals (seeds) are asked to invite a number of peers from a specified population to be screened for a study. The *seeds* are often given a certain number of enrollment slips or coupons to provide to their peers. YBLMSM and YBLTW social networks are likely to overlap. However, limited studies have sought to use RDS to recruit these overlapping populations. Tailored strategies for youth, such as incorporating RDS *seeds* from social networks, may improve the identification and recruitment of HIV-infected and high-risk HIV-uninfected YBLMSM and YBLTW and identify individuals with comorbid factors, including substance use, that may impact engagement and retention in care and prevention [37].

With 94% of Black teens and 99% of lesbian, gay, bisexual, and transgender young adults owning or having access to a smartphone [38], mobile-based interventions have the potential to engage youth in HIV prevention and the treatment cascade [39]. The benefits of mobile apps to engage gay and bisexual men have been documented by other researchers [40-42]. However, few have tried to simultaneously address both the HIV prevention and treatment cascade and substance use behaviors that may coexist among YBLMSM and YBLTW. Further, engagement in prevention and treatment has been a challenge even for prior studies that have effectively demonstrated short-term changes in condom use behavior [43]. Peer support (or coaching) with a mobile app has the potential to improve engagement through interactive motivational feedback around HIV and substance use risk. Such approaches have the capacity to screen adolescents for HIV risk and provide brief substance use interventions that are a flexible, low-intensity strategy that empowers youth and connects them to earlier access to HIV treatment, prevention services, and reduction of specific risks identified. This may be prudent given the prior studies that have demonstrated that community-based mentoring and peer support effectively build resilience and address barriers to care, including stigma and homophobia in YBLMSM and YBLTW [44-46]. To date, however, few studies have examined such approaches among YBLMSM and YBLTW living in the United States.

Objectives

The goal of this paper is to describe a study protocol to (1) identify and recruit YBLMSM and YBLTW who are at risk or living with HIV in Baltimore, MD; Philadelphia, PA; and Washington, DC, and (2) to assess the efficacy of a coach-based mobile-enhanced intervention (MEI) compared with standard of care (SOC) to increase successful engagement and retention in HIV care, prevention, and substance use treatment for YBLMSM and YBLTW living in the 3 Mid-Atlantic cities. Ultimately, we are interested in using the HIV care and prevention continuum [2,47] to evaluate strategies to identify and engage YBLMSM and YBLTW who are at risk or living with HIV, while simultaneously addressing substance use comorbidity [48]. The manuscript focuses on the development and formative work of this study and a summary of the protocol.

The research protocol described here is a collaboration between the Johns Hopkins Schools of Medicine (Harriet Lane Clinic) and Bloomberg School of Public Health, the Public Health Management Corporation, and 3 collaborating sites: Children's Hospital of Philadelphia (CHOP), Children's National Hospital, and Whitman-Walker Health.

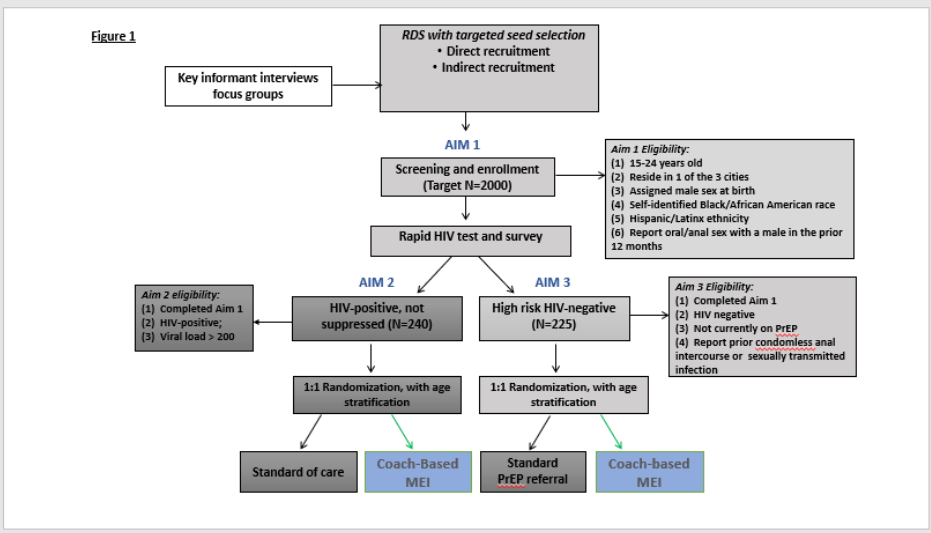
Methods

Study Design

This study uses a multiphase mixed methods design [49]. The first phase is an exploratory, incorporating formative, qualitative research with key informant interviews (KIIs) and focus group discussions (FGDs). These KIIs and FGDs are intended to inform further development and refinement of the methods utilized in the study, including questionnaire content, components of the intervention, and topics explored in the embedded qualitative research [50].

The protocol covers the 3 aims of the study. The first aim is to identify and recruit YBLMSM and YBLTW living in the 3 Mid-Atlantic cities into the prevention and treatment continua. The second aim is to use an embedded randomized controlled trial (RCT) to examine the efficacy of a coach-based MEI to achieve sustained retention and engagement in HIV care among youth living with HIV who are not virally suppressed. The third aim is to use an embedded RCT to examine the efficacy of a coach-based MEI to achieve uptake of and adherence to PrEP and other preventive behaviors (eg, *protected* sex acts) among youth at elevated risk for HIV infection. Both aims 2 and 3 examine identification, referral, and engagement in substance treatment services. The outline of the study design is shown in Figure 1.

Figure 1. Study flow diagram. MEI: mobile-enhanced intervention; PrEP: pre-exposure prophylaxis; RDS: respondent-driven sampling.



1) 15-24 years old; (2) reside in 1 of the 3 cities; (3) assigned male sex at birth; (4) self-identified Black/African American race; (5) Hispanic/Latinx ethnicity; and (6) report oral/anal sex with a male in the prior 12 months.

Study Setting

The study is being conducted in the following US cities: Baltimore, MD (Johns Hopkins University); Philadelphia, PA (CHOP); and Washington, DC (Children's National Hospital and Whitman-Walker Health). Each city experiences high rates of HIV among YBLMSM and YBLTW (aged 15-24 years) [3].

Formative Research Focus Groups and KIIs

Focus groups and KIIs were used in the formative phase for the purpose of adapting the study tools, identifying key components of the intervention, and developing the intervention structure. The formative phase was conducted between February 2017 and May 2018. First, 3 focus groups were conducted in Baltimore, MD, to modify and adapt an app for the MEI to meet the needs of YBLMSM and YBLTW. Following focus groups, key informants (KIs) were interview-identified across all 3 cities to inform the refinement of the interventions proposed by the focus groups and to identify topics to be explored in the qualitative interviews.

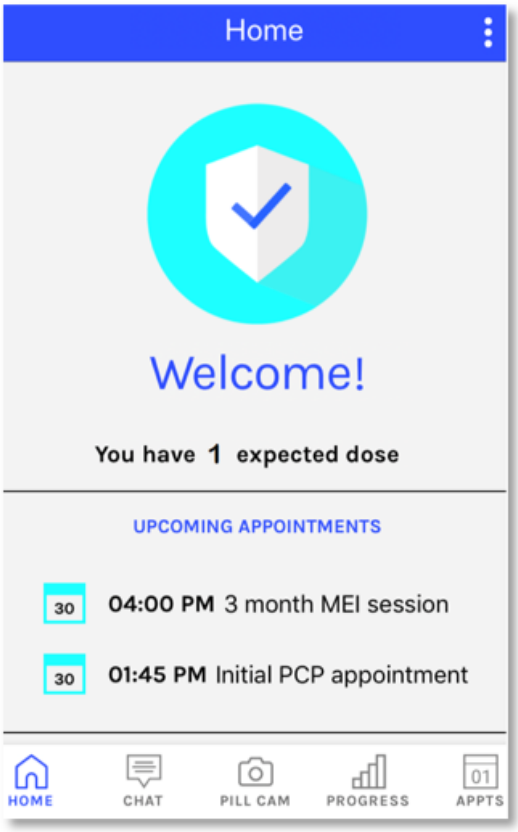
Formative Research Study Sample

Participants in the focus groups were eligible to participate if they currently resided or worked in Baltimore, MD, were aged 15 to 24 years, and either self-identified as YBLMSM or YBLTW. Participants of focus groups were recruited through flyer advertisements or provider referrals. KIs and focus group participants were reimbursed US $35 for participating. KIs included young adults with either a social or mentoring role in the community or someone who worked as a case manager, community outreach specialist, or volunteer. KIs were eligible to participate if they currently resided or worked in Baltimore, MD; Philadelphia, PA; or Washington, DC, and were identified by LGBTQ-serving organizations as persons who were in or around the target age range (18-24 years) and served as YBLMSM and YBLTW or a part of the community. Organizations who referred to KIs were asked to confirm that the KIs fit the eligibility criteria of the study.

Data Collection for Formative Research

The 3 focus groups lasted for 45 to 60 min and occurred in Baltimore, MD, only, with an average of 3 participants per group. Facilitation of the focus groups was done in collaboration with emocha Health Inc, a Baltimore-based company that assisted with the development of the mobile app. The goal of the focus groups was to identify key areas of focus for the intervention, mobile app components, and to elicit feedback on wireframes (Figure 2). Wireframes were based on areas developed by emocha Health, Inc for other adherence studies at a seventh-grade literacy level or lower [51]. Additional feedback was provided by an established sexual minority youth advisory board at the Philadelphia site.

Figure 2. Wireframe of mobile app. MEI: mobile-enhanced intervention; PCP: Primary Care Provider.



KIs elicited feedback about the intervention from youth or service providers from all 3 cities. The one-time, face-to-face, video or telephone interview lasted approximately 45 min. Semistructured interview guides were created to facilitate discussion around the topics of community and societal barriers to accessing HIV treatment and prevention among YBLMSM and YBLTW and strategies (eg, navigator, coach, and mobile app) that could be used to address barriers. Participants were then asked to provide feedback on specific components of the mobile app developed by emocha Health, Inc around potential

use and functionality. Example questions used in the focus groups and KIs included, "Rank the following features that would be helpful to you (or a YBLMSM or YBLTW aged 15 to 24 years) in improving your (their) health and following up with your (their) medical care: (1) goal planning for medications, (2) adherence reminders, (3) adherence support (rewards or points for positive adherence, coach support), (4) pill cam, (5) progress calendar; (6) personalized health information or text messages, and (7) general information (information about testing, condoms, resources, housing, and insurance). Why did you select (insert top choice) as your top choice?"

Data Analysis

Focus groups and interviews were audio-recorded and transcribed verbatim by an independent transcription company. Initial codes were identified from the interview and focus group guides developed by our research team. The codes were then refined and elaborated during the process of analysis using the constant comparison method [52].

Using a systematic approach to further validate and connect categories continued until the point of data saturation [53]. Grouped and categorized codes were then examined for emergent themes [49]; approximately 10% (n=3) of transcripts were double-coded and then reviewed for intercoder reliability or consistency to ensure high coder agreement (Kappa>0.80). Transcripts were reviewed using NVivo 11 software and included analyses based on the presence of identified codes and emergent concepts.

A total of 10 youth participated in the focus groups, and 18 KIs participated in formative interviews. Focus group participants suggested that the app include the following components: (1) goal planning for ART adherence and substance use treatment, (2) time reminders, (3) adherence reminders, and (4) adherence support (rewards or points for achieving optimal adherence). Findings from key interviews have been described elsewhere [54]; however, KIs recommended that the study allow for a longer follow-up time (greater than 4 weeks) for coupons to ensure engagement around recruitment, and suggested that the app has rewards for achievement. KIs suggested that the intervention focused on values (health priorities and personal goals), medication initiation and adherence, medical appointments, alcohol or drug use, and sexual health. The KIs suggested that the intervention should be flexible with bidirectional support with a coach, using multiple methods (eg, app, text message, and telephone calls), and the coach must be a peer or close to the population to enhance engagement with the intervention.

Clinical Trial Methods

Aim 1

Sample and Setting

The first aim of this protocol is to identify and recruit YBLMSM and YBLTW who are at risk or living with HIV in Baltimore, MD; Philadelphia, PA; and Washington, DC, using RDS with targeted seed identification. This protocol focuses on participants who are (1) aged 15 to 24 years, (2) reside in the 3 study cities, (3) assigned male sex at birth, (4) self-identified Black/African American race or Hispanic/Latinx ethnicity, and (5) report oral or anal sex with a male in the prior 12 months. We included youth assigned male sex at birth, including both transgender and gender-expansive youth as well as nonbinary youth, given the gender diversity, dynamic, and fluidity of gender identity during adolescence. In addition, adolescents may be at varying places along the gender transition spectrum and may or may not identify as male or transgender [55].

Recruitment

Participants are recruited using RDS with targeted seed selection. As part of aim 1, we aimed to compare direct and indirect targeted seed selection methods for reaching at-risk youth (behaviorally at risk for HIV acquisition or living with HIV and virally unsuppressed). Direct seed selection consists of informational flyers directly given to youth from study staff at a clinical site or at a community-based organization or in-person event (eg, house ball, pride, or community informational session). Indirect seed selection consists of informational flyers posted at clinical sites that serve LGBTQ youth or at the offices of community-based organizations. Indirect seed selection also includes a web-based approach that consists of electronic advertisements placed on webpages and social and sexual networking sites frequented by YBLMSM (eg, Jack'd, Black Gay Chat, and Grindr; Figures 3 and 4). A link on the web-based advertisements directs potential participants to the study landing page where they can leave their information for staff to contact them about participating [56]. The staff maintain the page and rotate images frequently to maintain engagement. Staff return all web messages within 48 hours.

RDS is a chain-referral sampling method that is typically used to approximate a probability sample of populations when sampling frames are unavailable [57,58]. For the purpose of this protocol, RDS is used to recruit behaviorally at-risk youth to status-dependent RCTs. Each seed was asked to participate in the study and to invite up to 5 peers from the target population to be screened for study eligibility. Unlike other HIV research, our goal is not to approximate a probability sample to produce population-based estimates but to investigate associations with risk behaviors and to identify participants who could be enrolled in the RCTs.

As recommended during formative research, this study uses electronic coupons (e-coupons) to facilitate the distribution of study coupons, given the challenges youth may face in physically meeting with peers to distribute paper coupons (as had been done previously). At the initial visit, a staff member meets with a participant, brainstorms about who to distribute coupons to peers, and provides instructions for the distribution of e-coupons using cell phones. The staff member provides a unique participant web link to the participant, which they then use to send their e-coupon to peers, including friends and social contacts. The link takes the participant to a page where they can see and manage the sharing of their e-coupons with peers. During the visit, the participant is asked to send their e-coupons to their peers (electronic respondent-driven sampling [eRDS] recruit) and to verify receipt. The eRDS recruit (a person receiving the e-coupon) receives a text message informing them

that they have been invited to participate in a research study. The text message includes a unique numeric code, study telephone number, study site operating hours, and an expiration date (approximately 2 weeks after issuance). The recruit then contacts the study team to set up an appointment at the study site, at which point they are asked to provide their e-coupon to staff to initiate eligibility screening. The unique numeric code of the e-coupons permits the identification of linkages between *seeds* or recruiters and recruits in the data. E-coupons omit any sensitive information about participating in an HIV-related study, though *seeds* or recruiters and peers can discuss this verbally. Participants who are unable to distribute e-coupons or who choose not to use e-coupons are provided paper coupons for distribution.

Figure 3. Web-based Flyer.

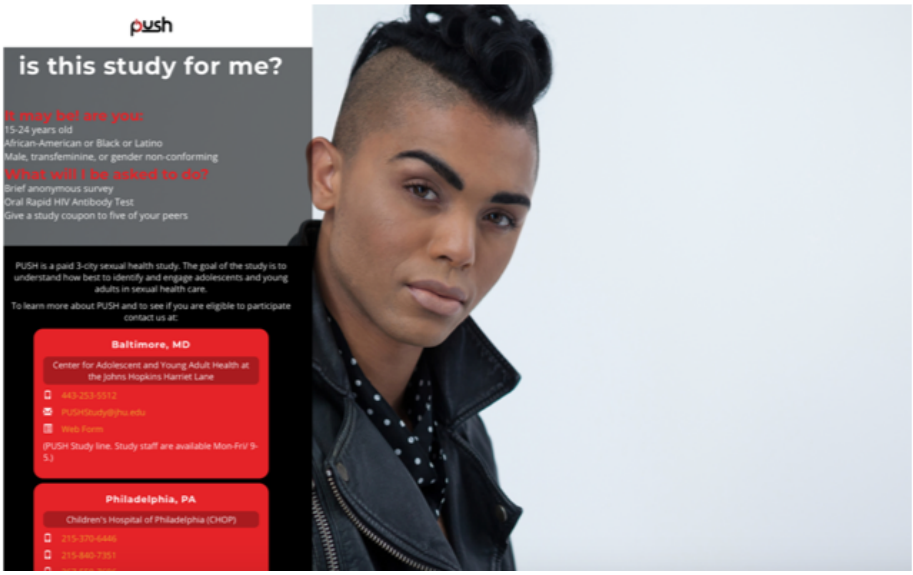
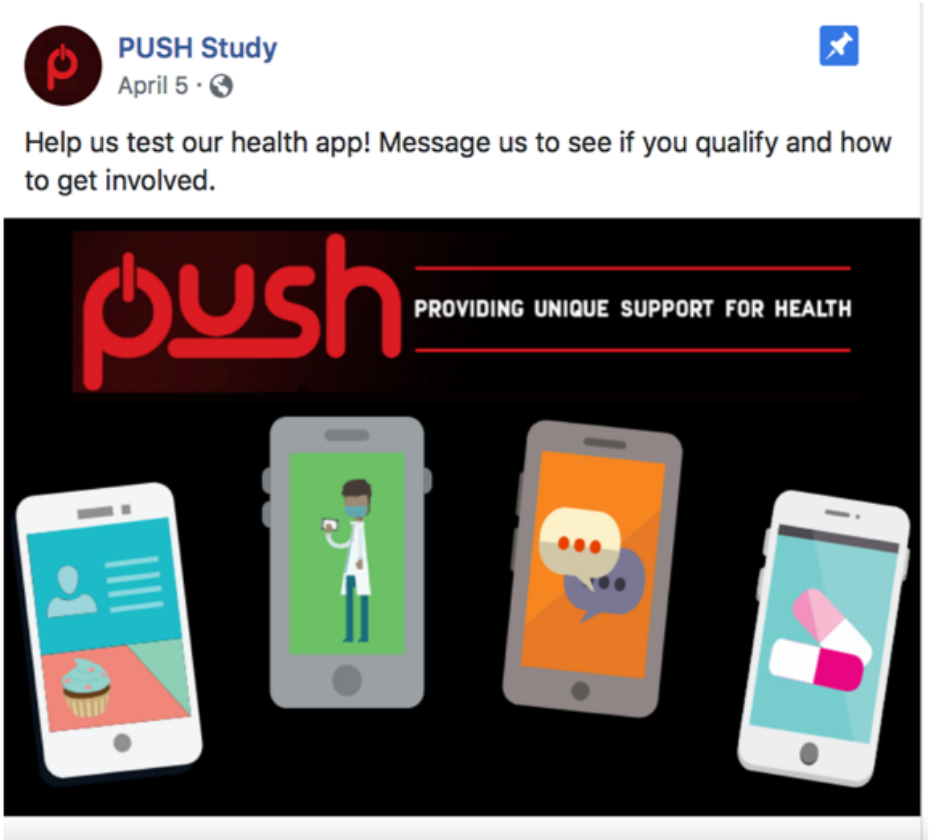


Figure 4. Example of Facebook/Instagram.



Study Activities

Participants, including both *seeds* and recruits, are provided the opportunity to complete a survey and a rapid HIV testing (OraQuick Advance or INSTI). The survey includes measures of key demographics, social network characteristics, HIV testing and diagnosis history, substance use, and history of PrEP use

(Textbox 1). Skip patterns are used to reduce the number and complexity of the questions. All data measures are captured in the same data system that is designed for RDS data collection and tracking. Data are tracked with a unique study ID only and are not associated with participant contact information.

Participants are asked to return in 2 weeks for coupon payment, to complete a second survey that asks about their social network and in what context coupons are provided, and to participate in a booster RDS training where they spend additional time with staff reviewing techniques and strategies to promote the distribution of coupons [59]. Participants are reimbursed US $5-15 per peer recruited peer (dependent on site).

Textbox 1. Study domains and measures.

Demographic measures

- Age, gender identity, marital status, education, annual income, race and ethnicity, health insurance status, housing, and employment status

Respondent-driven sampling

- Network size and characteristics, utilized for respondent-driven sampling weighting

Internet or mobile phone use

- Type of phone, data plan, and frequency of use; loss of plan; and other family members who have access to the phone

Venue use

- Information on physical venues where participants frequent will be collected; venues will be included to assess overlap between physical and web-based seed networks

HIV testing and care history

- Frequency of HIV testing in the past year, date of most recent HIV test, and receipt of HIV test results

HIV continuum

- Self-reporting HIV infection; current engagement in care, including antiretroviral treatment; adherence; and self-reported viral load status

Knowledge of pre-exposure prophylaxis (PrEP) and postexposure prophylaxis (PEP)

- Knowledge, perception of, and history of PrEP and PEP use

Sexual matrix module and sexual risk behavior

- Sexual attraction, identity, and behavior; 7-item question HIV Incidence Risk Index for men who have sex with men (MSM) males only [60,61]; information on number of partners and frequency and types of sexual acts; network of the sexual contacts; location of where sexual experiences occurred; and perceived sexual risk for sexually transmitted infections, including risk for HIV

Health care use

- Health care and services utilization and engagement and trust between the clinician and patient

Stigma and mental health

- Self-stigma (internalized homo-negativity) and HIV stigma (with consideration of impact on HIV testing and adherence) adapted from Herek et al [62,63]; mental health will include lifetime and recent history of depressive symptoms and anxiety, using the Patient Health Questionnaire-4 [64], post-traumatic stress disorder (Child Post-Traumatic Stress Disorder Symptom Scale) [65], and experiences of discrimination [66]

Social environment

- Outness Inventory [67]; intimate partner violence, victimization, and perpetration (Safe Dates instrument) [68]; sexual guilt (Revised Mosher Sex-Guilt Scale) [69]; lesbian, gay, bisexual, transgender, and questioning (LGBTQ) victimization [70]; and social context (perceived parental support and religious environment) [71]

Substance use

- Car, relax, alone, forget, friends, and trouble (CRAFFT) six-item substance use screen and a modified Time Line Followback assessing days of use of various substances [72,73]

Engagement in the lesbian, gay, bisexual, transgender, queer (LGBTQ) community

- Measures of strength of engagement and connection in the LGBTQ community

Coach-Based MEI for Youth Living With HIV

The second aim of the protocol is an RCT to examine the efficacy of a mobile-enhanced coach-based intervention to achieve sustained retention and engagement in HIV care among youth living with HIV who are not virally suppressed.

Aim 2

Study Sample

YBLMSM or YBLTW, recruited into aim 1, who are identified as HIV-positive (previously diagnosed with HIV—self-report of HIV-1 and confirmed viral load, or newly diagnosed—no prior history of HIV and rapid HIV test positive) are invited to participate in the RCT of aim 2 of the study. Additional eligibility includes not virally suppressed; no plan to relocate in the next 18 months; not enrolled in another HIV treatment intervention; and currently own or have access to a cell phone, private tablet, or laptop. Potential participants are provided information about the study, consented, and a blood sample for the viral load is obtained (if no recent viral load within 3 months was documented in the medical chart). Participants with an HIV-1 viral load>200 copies/mL are eligible to participate in aim 2. We aim to recruit 240 YBLMSM or YBLTW living with HIV who are not virally suppressed.

Study Procedures

After enrollment, participants complete a baseline survey and are randomized (1:1) to 1 of 2 study arms: coach-based MEI or SOC. Randomization to the intervention arms is stratified by site; age group, to yield a balanced randomization between younger (aged 15-19 years) and older (aged 20-24 years) age groups; and enrollment site.

SOC

Participants randomly assigned to the SOC arm are provided information about and referrals for HIV care and/or prevention. They return to the research setting every 3 months to complete surveys and conversation with assigned study personnel. The focus is on active listening, with no attempts to direct goal setting; screening, brief intervention, and referral to treatment (SBIRT); or motivational interviewing (MI), as discussed below. Personnel are encouraged to refer to local clinical resources, help with participant care navigation, and case management services at each follow-up visit, as needed.

Coach-Based MEI

The coached-based MEI is a tailored and enhanced case management strategy that serves as the primary intervention for participants with unsuppressed HIV viral load. Individuals randomized to the coached-based MEI receive weekly telephonic and app-based support and a structured face-to-face meeting every 3 months, augmented by the ongoing implementation of the study's mobile app. Telephonic and in-person supportive consultations are goal focused and designed to enhance linkage, ART initiation, adherence, and retention in care for MSM diagnosed with HIV [74-76]. The MEI coach is trained in and utilizes Rogerian listening skills, MI, SBIRT for substance use, and personal health goal setting to best support assigned participants [77-81]. It is based on the case management protocol 078 of the HIV Prevention Trials Network (HPTN) [82], emphasizing routine engagement around health behaviors and goals. To meet the needs of youth, the team modified the approach to adapt it for YBLMSM and YBLTW living with HIV and to incorporate the mobile app and MI components.

Training and Selection

MEI coaches were hired based on previous work experience in the MSM community, HIV services (eg, outreach, testing, and case management), interest in aiding research, and ability to communicate effectively with the target population. Representation of the MSM, Black, and Latinx communities was encouraged in the job posting process.

MEI coaches received an initial intensive 16-hour training including (1) introduction to study (2 hours); (2) developmental considerations in cognitive and emotional processing in teens and young adults (1 hour); (3) barriers to PrEP uptake, HIV ART adherence, and HIV risk reduction (1 hour); (4) SBIRT, including screening tools for alcohol and drug use, and effective interviewing about substance use (1 hour); (5) discussion on cultural competence and social determinants of health in case management with YBLMSM and YBLTW (1 hour); (6) mobile app and encouraging engagement with participants (1 hour); (7) study fidelity and data recording expectations (2 hours); (8) didactics and group practice on goal setting and health behavior change (1 hour); and (9) MI components on MI spirit, stages of change, core skills (eg, guiding, open-ended questions, affirmations, reflections, and summarizing), collaborative goal setting, *rolling with resistance*, and repeated role-play (6 hours).

MEI coaches receive ongoing training and support during their continued involvement in the study. Bi-weekly, hour-long videoconference supervision on MI application, goal setting, and troubleshooting are provided remotely by a psychologist with expertise in MI training, substance use, and HIV care. In-person, telephonic, and app-based participant communications, successes, and barriers are discussed as well as topical trainings based on coach needs, MI skills, goal setting, and substance use. The MEI coaches routinely audio-record face-to-face visits with participants assigned conditions, and the supervising psychologist provides individualized written and verbal feedback on each recording on the use of MI and goal-setting techniques, as applied to the individual's circumstances as well as fidelity to the study intervention.

Study Intervention

The intervention is administered by a trained MEI coach and includes substance use screening brief interventions and ongoing monitoring throughout the prevention and treatment care cascade [72]. Coaches begin in the initial face-to-face visit with building rapport, explaining the intervention, and identifying personal and health goals. Health goals focus on medication adherence, health care engagement and satisfaction, substance use, and sexual health. Coaches then map out and help the participant prioritize each goal. After the initial question-answer period and establishment of goals, the MEI coach develops an individually tailored plan that is designed to utilize self-determination theory [83] and the Integrated Theory of Health Behavior Change [84] to facilitate the adoption and maintenance of health behaviors. The approach is centered on identified participant goals and values and care engagement,

utilizing a card-sort procedure to help prioritize participant goals for each session [77]. Participants who score positive on the CRAFFT (car, relax, alone, forget, friends, and trouble) and Alcohol, Smoking, and Substance Involvement Screening Test are provided with prevention psycho-education around substance use risks [72,73,85]. Participants who score 2 to 3 on the CRAFFT are encouraged to develop a change plan to reduce substance use and scheduled for additional intervention sessions. These cutoffs were used because a CRAFFT score of 2 or higher is optimal for identifying any substance-related problem and an SUD (according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition criteria) [86]. Coaches subsequently attempt to link participants who score above 4 to substance use services. Participants who describe sexual risk (eg, condomless anal sex) are also provided psycho-education around sexual risk and PrEP. Coaches help participants develop strategies to avoid substance use and sexual risks in the future.

At the core of the coached-based MEI approach are supportive services such as navigation, adherence counseling, and tailored support for care engagement and treatment adherence for persons living with HIV. This intervention focuses on 3 steps in the support process: MyCare (steps 1 and 2) and MyHealth (step 3). Participants who are living with HIV start with MyCare (step 1) to support the decision to (re-)initiate HIV care. This includes the use of MI to help orient the client toward seeking and initiating care. MyCare (step 1), which is modeled after life steps, a single-session intervention grounded in cognitive-behavioral principles, is at the core of several successful ART adherence interventions [12,87,88]. MyCare (step 2) adds to this evidence-based approach by recognizing that adherence to medications is a personal choice grounded in a variety of behavioral and psychosocial domains. MyHealth (step 3) is based on the premise that a patient engaged in self-management and supportive strategies will feel empowered to take ownership of their own health care needs.

The face-to-face visits consequently address psycho-education about HIV risk, HIV and ART, planning and problem-solving to access and maintain a steady supply of medication, formulating a daily medication schedule, cues for pill-taking, coping with side effects and/or other participant concerns, developing a plan to mitigate side effects and responses to slips in adherence (if applicable), and engaging around condom use and/or limiting sexual risk behaviors. Counseling is tailored to the participants' specific needs and case management or navigation needed.

Telephonic and app-based check-ins between the MEI coach and participants are conducted to maintain rapport, open communication, review progress on personally identified goals, help troubleshoot challenges that may arise, and provide reminders for upcoming face-to-face visits. The app is used to facilitate communication around medication adherence, medical visit completion, video chat, and bidirectional communication. The MEI coach will determine the participant's desire for support, and the frequency and schedule of messages. It is the aspirational goal of the study to have the MEI coach have weekly contact with participants; however, this is often not realistic for all participants. For example, some participants will embrace weekly check-ins, others prefer to engage more intermittently, and the remaining participants may experience situational or motivational barriers that may interfere with engagement. MEI coaches may need to utilize MI strategies to explore readiness to engage in telephonic check-ins and study visits and troubleshoot barriers that may arise (Table 1), and re-engagement needs to be pursued by the MEI coach. MEI coaches seek to check-in with participants weekly (at a minimum), and participants are encouraged to attend face-to-face follow-up coach visits at 3, 6, and 12 months. During these face-to-face visits, coaches will work with the participant to review, motivate, and reinforce personal life events, health care engagement, review substance and risk reduction goals, and problem-solve. Using this MI approach, the participant is thus empowered to take the lead with recommendations and guidance from the MEI coach. Permission is sought to audio-record each initial and follow-up study visit for the purpose of assessing study fidelity and providing routine, ongoing feedback to the MEI coach. The recording is at the discretion and informed consent of the participant and the MEI coach. Ad hoc telephonic and in-person support is also provided by the MEI coach, as requested by the participant. An MEI coach, at any time may help, for example, with referral to behavioral health, job resources, community support resources (eg, a food bank), provide supportive listing, or help arrange any requested sexually transmitted infection testing.

Table 1. Motivational interviewing approaches to address level of interest in telephonic engagement.

Participant comments	Stage of change	MEI[a] coach approach
Agreement: "Sure, I wouldn't mind texting each week."	Action	Reinforcement, summarize: "Great, I will make sure I will check-in by text each week, or more if wanted by you."
Barrier: "That would be good, but my phone sometimes cutoffs if I don't make my bill."	Determination	Summarize, empower: "I understand. I will try to text each week, and occasionally you may not have cell service. Any ideas of what we could do to stay in touch if your phone loses service?"
Ambivalence: "I'm not sure, I mean I wouldn't mind, I guess."	Contemplation	Paraphrase, elicit, affirm: "I hear you might be willing to consider this, and you might not be sure… (Pause...momentary wait...and follow-up if no response)… I have definitely worked with some people who were wary about the check-ins, is there anything about this you might not be thrilled about?"

[a]MEI: mobile-enhanced intervention.

Fidelity

Face-to-face coached-based MEI visits will be recorded. A standardized fidelity checklist will be utilized by the supervising psychologist to quantify discussion of topic domains, rating the domains on a 3-item Likert scale (0=none, 1=partial discussion, and 2=focused discussion) with provided anchors. The domains for coverage during an MEI coach visit are (1) taking medication as prescribed, (2) attending medical appointments, (3) experience at the health provider's office, (4) encouraging participants' use of the MEI mobile app, (5) participant's actual engagement with the mobile app, (6) alcohol or drug use, (7) sexual health, and (8) role of values in participants' health decision making. A total of 20% of all recorded visits will be reviewed for overall fidelity, seeking a representative sample across MEI coaches, and follow-up visits (eg, baseline and 3-months) across the course of the study. Interrater reliability will be conducted by a coworker of the supervising psychologist trained in the intervention and research methods. MEI coaches will also complete their own fidelity assessment after each MEI coach face-to-face visit, which will help to regularly refresh and reinforce the core elements of each study visit. Data will also be collected from study participants about what topics were covered in their study visits. MEI coaches will also log all study contact with each participant on a secured study record, allowing for monitoring and feedback on the frequency of telephonic encounters.

Coach-Based MEI for Youth at Risk for HIV

The third aim is to use an RCT to examine the efficacy of a mobile-enhanced coach-based intervention to achieve uptake of and adherence to PrEP and other preventive behaviors (eg, *protected* sex acts) among youth at elevated risk of HIV infection.

Aim 3

Study Sample

This sample will be composed of YBLMSM or YBLTW recruited into aim 1, who test negative for HIV but are not currently on PrEP, and report either engaging in condomless anal intercourse or a prior history of a sexually transmitted infection. Additional eligibility includes no plan to relocate in the next 18 months; not enrolled in another PrEP behavioral intervention; and currently own or have access to a cell phone, private tablet, or laptop. Potential participants are provided information about the study and must consent to participate. We aim to recruit 225 YBLMSM or YBLTW at risk for HIV.

Study Procedures

After enrollment, participants complete a baseline survey and are randomized (1:1) to 1 of 2 study arms: coached-based MEI or SOC. Randomization to the intervention arms is stratified by site; age group, to yield a balanced randomization between younger (aged 15-19 years) and older (aged 20-24 years) age groups; and the enrollment city. After each participant is identified, they are provided with their assigned treatment assignment.

SOC

Participants randomly assigned to the SOC arm in the at risk for HIV group receive a similar structure as those with uncontrolled HIV. Initially, they are provided information about HIV prevention strategies and the schedule for follow-up data assessments. During quarterly meetings, a brief check-in conversation and active listening is conducted without the use of SBIRT, MI, or goal-setting, and participants are referred, if needed, to local clinical or community assistive and services at each follow-up visit.

MEI Coach Intervention

The focus of the Providing Unique Support for Health (PUSH) study is to engage individuals at risk for HIV into prevention and care. The approach is the same as aim 2, modeled after life steps [12,87,88] and based on the case management protocol 078 of the HPTN [82]. It is tailored to the prevention needs of the youth. As such, during the first step, the coach uses MI to orient participants and increase their readiness for preventive engagement. The counseling session addresses psycho-education about HIV risk; planning and problem-solving for mitigating risk, including addressing coexisting substance use; coping with side effects and adherence of PrEP; and/or other participant concerns, developing a plan to address slips in PrEP adherence (if applicable) or condom use. Coaching is tailored to the participants' specific needs and case management or navigation needed. As with the second aim, randomly assigned participants will be requested to meet with their MEI coach every 3 months and have weekly telephonic check-ins, to review progress on personal goals, risk reduction, and help to troubleshoot factors that may increase HIV risk or personal goals. The MEI coach will utilize MI, SBIRT, active listening, and goal-setting in face-to-face visits, and telephonically will check-in on their lives, their goal progress, and app usage. MI strategies will be utilized to address motivational and situational barriers to study engagement in person or telephonically (Table 1).

Similar to the second aim, this MEI coach intervention focuses on 3 steps in the support process: MyCare (Steps 1 and 2) and MyHealth (step 3). MyCare (Step 2) adds to this evidence-based approach by recognizing that uptake of PrEP or prevention services is a personal choice grounded in a variety of behavioral and psychosocial domains. MyHealth is based on the premise that a patient engaged in self-management and supportive strategies will feel empowered to take ownership of their own health care needs. The MEI coach will determine the participant's desire for support and the frequency and schedule of messages. For example, some participants embrace engagement intermittently, whereas other participants delay engagement and need to be taken through the engagement steps again. Participants are provided with as much or as little coaching as needed using this flexible approach, but the MEI coach will check-in with participants telephonically weekly (at a minimum), and participants are requested to attend face-to-face follow-up coach visits at 3, 6, and 12 months. During these visits, the coach will review participant's progress toward personal and health goals, motivate and reinforce treatment engagement, review substance and risk reduction goals, and help problem-solve any obstacles that may have arisen. Using

this approach, the participant is thus empowered to take the lead with recommendations and guidance from the MEI coach. Participants receive ongoing screening for sexual risk and substance use, and the coach's approach is modified based on self-reported needs.

The study infrastructure for supporting and maintaining the MEI coach will be duplicated for the third aim. MEI coaches will receive remote bi-weekly support, instruction, troubleshooting, and feedback from the supervising psychologist, focusing on the delivery of MI, goal-setting, and SBIRT. Audiotaped recordings will be conducted during face-to-face visits, with the informed consent of the participant and discretion of the MEI coach, and will be reviewed by the supervising psychologist for feedback and assistance to the MEI coach and to track study fidelity. Likewise, participants and MEI coaches will complete fidelity assessments postvisit to reinforce study aims, prevent intervention drift, and provide additional data about the intervention delivered.

Data Collection for Aims 2 and 3

The PUSH study uses a built-in randomization engine adapted from previous studies [89]. The allocation between intervention and control arms is determined randomly by the engine, where each round comprises 2 intervention and 2 control assignments that are linked to the stratification factors of site and age group. Once a round is completed, a new round begins.

Participants are asked to participate in research visits at 0, 3, 6, 9, 12, and 18 months (exit interview). This visit schedule aims to ensure frequent contact and to minimize attrition. Laboratories and study-related activities are described in Table 2. Surveys provided at baseline (Textbox 1) are re-administered at each follow-up with additional questions focused on ART, PrEP, barriers, and facilitators to adherence.

Table 2. Study visits and associated laboratory tests.

Tasks	Visits					
	Baseline	3 months	6 months	9 months[a]	12 months	18 months
Complete a survey	✓[b]	✓	✓	✓	✓	Exit interview
Provide blood for HIV-1 RNA viral load testing (aim 2) or HIV-1 antibody testing (aim 3)	✓	✓	✓	—[c]	✓	—
Provide urine for drug testing	✓	✓	✓	—	✓	—
Update locator information	✓	✓	✓	✓	✓	—
Meet with MEI[d] coach (intervention only)	✓	✓	✓	✓	✓	✓
Medical chart review (research staff only)	✓	✓	✓	✓	✓	✓
Compensation, US $	50	50	50	10 check-in via phone; 25 survey	50	25
Participate in an in-depth interview (selected participants)	✓	—	✓	—	✓	—
Compensation, US $	25	—	25	—	25	—

[a]9-month visit constitutes either a brief phone check-in (5 min) or in-person survey (15 min).

[b]Data collected at this time point.

[c]Data not collected at this time point.

[d]MEI: mobile-enhanced intervention.

Sample Size Considerations

We aim to recruit up to 2000 YBLMSM and YBLTW to be screened for eligibility for aims 2 and 3. We conservatively estimate that 15.00% of the RDS recruited sample will be HIV-infected and not virally suppressed, given an HIV prevalence of 25% to 40% among YBLMSM and YBLTW across the sites and as many as 60% of HIV-infected YBLMSM are undiagnosed [4,9].

We expect a 15.0% loss to follow-up over 1 year in aim 2. Starting with n=240 will yield an effective sample size of 204 individuals in total, or 102 in each group, available for analysis in aim 2. A total estimate of n=200 will be enough to detect an average increase in the viral suppression proportion over the 3 follow-up visits of 16.0% from 24.0% assumed in the control arm to 40.0% in the coached-based MEI arm (odds ratio, OR 2.03), assuming a power of 85.0%. We expect a slightly greater loss to follow-up (20.0% loss to follow-up) in participants in aim 3. Starting with n=225 will yield an effective sample size of 180 individuals in total or 90 in each group. We estimate that a total of 180 participants (90 per group), and assuming a 15.0% average rate on PrEP in the control arm, we can detect an average increase of 14.0% to 29.0% (OR 2.31) with power 85.0%. Lost to follow-up estimates are based on the team's prior work with this population.

Data Analysis

Aim 1 analyses are descriptive and include baseline characteristics related to sociodemographic characteristics, HIV infection, and sexual behavior of the YBLMSM and YBLTW samples across all sites as well as stratified by site. Descriptive tables with unweighted estimates and Pearson chi-squared tests

for significance are used to compare age, web-use and venue attendance, and other characteristics of each recruited seed type.

To compare the efficiency of *seeds* from direct versus indirect seed selection in the recruitment of HIV-positive or at-risk youth, we use the RDS statistical package developed by Schonlau and Liebau [90]. This permits an assessment of the overlap of networks across seed types and across recruitment sites. Efficiency is assessed through recruitment diagnostics, including coupon return rate, homophily, the mean number of recruits, and recruitment depth per seed type. This approach also allows us to assess the time from recruitment activation through the achievement of target sample size and response rates. RDS weights will not be utilized in these analyses, as this aim focuses on descriptive sample proportions rather than producing population-based estimates. We will also examine the networks described by younger (aged 15-19 years) and older (aged 20-24 years) participants recruited from different *seeds* and use similar methods to understand the overlap of age groups across different networks.

The primary outcome for aim 2 is durable viral suppression (HIV viral load<200 copies/mL), and the secondary outcome is retention in HIV care (defined as documented 2 or more follow-up medical visits over 12 months, treated as a dichotomous variable). The primary outcome for aim 3 is self-reported PrEP use over 12 months in PrEP users, and the secondary outcome is self-reported condom use in PrEP nonusers. The overall approach is based on an intention-to-treat analysis with treatment assignment (eg, coached-based MEI vs SOC) being the primary independent variable for all models.

The success of the randomization process is measured by comparing the distribution of participant characteristics between the 2 groups at baseline. If the randomization process does not result in comparable groups, adjustment is made for group differences in the multivariable models. For aim 2, logistic regression is used to examine whether participants who receive MEI coach are more likely to be virally suppressed as well as retained and engaged in HIV care than participants in the SOC arm. Generalized estimating equations (GEE) are used to determine whether treatment assignment predicts differences in retention for the coached-based MEI versus the SOC groups using repeated measurements over a 12-month period. GEE is used for the longitudinal data as it adjusts for the intra-personal correlation of repeated measurements on the same individual and provides an estimate of the standard error that is robust to misspecification of this correlation structure.

For aim 3, to evaluate whether YBLMSM and YBLTW receiving coached-based MEI have greater uptake of PrEP over 12-months, a survival model is used to examine whether intervention assignment is associated with time to PrEP use. GEE is used to determine whether treatment assignment predicts differences in PrEP utilization and adherence over time for the coached-based MEI versus SOC groups using the repeated measures over the 12-month period [91]. For both aims, we explore trends in uptake and adherence to treatment or PrEP for the intervention group compared with the control group by including an interaction term between time from randomization and treatment assignment.

Going beyond the intention-to-treat approach, we will develop multivariate models stratified by age group (aged 15-19 years and 20-24 years) and include potential confounders and predictors such as prior exposure to case management and PrEP, sexual risk (low vs high), and other demographic variables. Additional models will be evaluated for possible dose-response relationships considering a measure of the level of engagement with the intervention and the frequency of app use. We will assess whether receiving coached-based MEI results in decreased substance use severity, by examining changes in mean CRAFFT scores (a measure of substance use severity) over time for the intervention group compared with the control group for each aim. CRAFFT scores will be treated as continuous dependent variables, and the models will adjust for intra-personal correlations between repeated measurements. Multivariate linear regression will be used to test for decreased severity at each follow-up visit, while controlling for identified confounders.

Modeling techniques have been selected based on the capacity to adequately handle the missingness of data. GEE models assume that the missingness is because of a missing at the random mechanism, which is a restrictive assumption. To address dropout, we use inverse probability weighting to relax this assumption of missing at random [92,93]. Other types of missing data will be handled using multiple imputations.

In-Depth Interviews

In-depth interviews are completed as part of routine follow-up visits (Table 2). Target enrollment for interviews is 6 participants (3 SOC and 3 MEI) per aim per site (total of 36). This total will be sufficient to reach informational redundancy across the 3 cities [53]. Interviews focus primarily on changes in self-reported sexual orientation and gender identity, mentorship and community experiences, health care navigation, barriers or facilitators to care or research, and substance use specific to YBLMSM and YBLTW. Initial analysis of the interview data follows the same procedure outlined in the formative data section.

Further analysis will allow for responses and interview themes to be compared across sites, time, participant's age, and other sociodemographic characteristics. The findings are presented to the team on an ongoing basis to provide insight into barriers and facilitators of engagement and intervention experiences over time. Participants are paid US $25 for each interview.

Consent and Human Subjects Considerations

Participants in this study go through a verbal consent process (paper or electronic) to enter the formative research, RDS survey, and/or enroll in the RCTs. Electronic consent displays on the screen before the web-based survey. Participants are prompted to provide their signature on the screen as an acknowledgment of consent. This study has obtained a waiver of parental permission for unaccompanied participants and adolescents seeking confidential services who are aged 15 to 17 years under 45 CFR Part 46.408(c), which is in line with local laws in (Maryland HG Section 20-102), Pennsylvania law (IRB SOP 505; Minors' Consent Act, 35, PS 10101), and Washington DC law (code 600.7). For youth aged 15 to 17 years

recruited through RDS that are not seeking confidential services, we will use *advocates* (trained social workers) who are independent counselors to work with each participant aged 15 to 17 years before and during the informed consent to ensure adequate comprehension of risks and benefits of participating in the research in Baltimore.

To provide adolescents with additional protections, a certificate of confidentiality has been obtained from the National Institutes of Drug Abuse (NIDA). All staff are trained on confidentiality, HIPAA (Health Insurance Portability and Accountability Act) privacy protections, cultural competency, adolescent counseling techniques, pre- and posttest counseling, mandated reporting, statutory rape laws (specific to the local context), and managing situations of child or sexual abuse. Adolescents who describe physical or sexual abuse or express concerns about mental health are linked to child protective or social work services to ensure their safety. This study was approved by the CHOP, the Children's National Hospital, and the Johns Hopkins School of Public Health institutional review boards.

Results

A total of 585 participants have been screened to date, with 450 (76.9%) enrolled. Recruitment monitoring showed that seed propagation was slow and reached low depths, frequently ranging from 1 to 3 waves of recruitment before stopping.

Table 3 summarizes the key demographic characteristics and reported substance use of baseline participants (N=402) and those who enrolled in aim 2 (n=36) and aim 3 (n=123). In summary, the median age was 21.6 years at enrollment, most participants identify as African American/Black (76.6%), 41 (10.2%) identify as transgender or female, 145 (41.5%) completed high school, and 145 (36.1%) had at least some college or technical education. One-quarter (97/402, 24.1%) reported having been without a place to stay in the last year, and most participants reported a history of substance use: alcohol (77.6%); cannabis (76.6%); and about a fifth reported use of other drugs including opioids, amphetamine, and cocaine (21.9%). Almost a quarter (n=100) reported engaging in transactional sex for a place to stay, money, or food. Moreover, 10% of the participants described having been forced to do something sexually (coerced sex, n=40) and 10.8% (n=43) described being forced not to use a condom during sex. Qualitative research is also ongoing. A total of 19 baseline interviews have been conducted within the 3 sites, with 9 interviews from aim 2 participants and 10 interviews from aim 3 participants.

Table 3. Demographic characteristics and substance use at baseline for participants.

Characteristics	AMSAB[a] participants (N=402)	Participants in aim 2 (n=36)	Participants in aim 3 (n=123)
Age (years), median (IQR)	21.6 (19.3-23.5)	22.9 (19.8-23.9)	20.7 (18.8-22.8)
Age category (years), n (%)			
15-17	42 (10.4)	4 (11.1)	17 (13.8)
18-24s	360 (89.6)	32 (88.9)	106 (86.2)
Race, n (%)			
Black/African American	308 (76.6)	30 (83.3)	91 (74.0)
Black/mixed	28 (7.0)	1 (2.8)	6 (4.9)
Latino/Black	26 (6.5)	3 (8.3)	12 (9.8)
Hispanic	30 (7.5)	0 (0.0)	9 (7.3)
Unknown	10 (2.5)	2 (5.6)	5 (4.1)
Gender, n (%)			
Male	347 (86.3)	30 (83.3)	108 (87.8)
Transgender	28 (7.0)	3 (8.3)	8 (6.5)
Female	13 (3.2)	2 (5.6)	1 (0.8)
Gender nonbinary or nonconforming	13 (3.3)	1 (2.8)	6 (4.8)
Sexual identity, n (%)			
Gay	255 (63.4)	25 (69.4)	86 (69.9)
Bisexual	88 (21.9)	5 (13.9)	24 (19.5)
Heterosexual	25 (6.2)	1 (2.8)	5 (4.1)
Queer	10 (2.5)	0 (0.0)	4 (3.2)
Pansexual	9 (2.2)	2 (5.6)	2 (1.6)
Other or questioning or missing	33 (3.2)	3 (8.3)	2 (1.6)
Highest level of education, n (%)			
<High school	89 (22.1)	12 (33.3)	29 (23.6)
High school graduate	167 (41.5)	13 (36.1)	50 (40.6)
>High school	145 (36.1)	10 (27.8)	44 (35.8)
Are you employed?, n (%)			
Yes	227 (56.5)	17 (47.2)	71 (57.7)
No	174 (43.3)	18 (50.0)	52 (42.2)
Been without a place to stay in the last 12 months, n (%)			
No	301 (74.9)	26 (72.2)	103 (83.7)
Yes	97 (24.1)	9 (25.0)	20 (16.3)
Substance use ever, n (%)			
Tobacco	154 (38.3)	26 (72.2)	35 (28.5)
Alcohol	312 (77.6)	29 (80.6)	97 (78.9)
Cannabis	308 (76.6)	30 (83.3)	100 (81.3)
Any other drugs (amphetamine, cocaine, opioids, sedatives, or inhalants)	88 (21.9)	15 (41.7)	27 (22.0)

[a]AMSAB: assigned male sex at birth.

Discussion

Principal Findings

The lack of data focused on identifying, recruiting, and engaging YBLMSM and YBLTW who are living with or at risk of acquiring HIV and have high rates of substance use contribute to health disparities and a public health crisis in this population.

Previous studies have described the use of RDS as an effective strategy to reach hard-to-reach populations. Some have also demonstrated challenges (eg, slow propagation) in reaching YBLMSM and YBLTW, though these studies have failed to examine different seed selection methods used in RDS [94]. The PUSH study allows us to examine assumptions about RDS seed selection methods and barriers to participating in research, which may help to inform future recruitment and sampling methods for interventions with sexual and gender minority youth.

This intervention study collects critical data on whether modification of an existing model for persons living with HIV can be used for YBLMSM and YBLTW living with HIV and those at risk for HIV. Evaluation of the PUSH study will address multiple gaps, including what components (eg, mobile app, telephone, and coach support) are needed to improve youth-based interventions to be more accessible and able to simultaneously address HIV treatment or prevention and substance use care. Although peer support is thought to be an additional strategy to improve access to care in this population [95-97], the gap in existing knowledge about the impact of coaches and/or peer-based strategies leaves prevention and treatment programs uncertain about their efficacy and effectiveness.

Limitations

There are limitations noted in this protocol. The focus population is only YBLMSM and YBLTW, limiting the generalizability of the findings. The focus groups were small and completed in 1 city, with feedback from 1 youth advisory board. We further clarified areas identified from focus groups in in-depth interviews across the cities, but this intervention may not be reflective of all the needs of YBLMSM and YBLTW. The protocol sample size estimates are based on high retention estimates.

Despite these limitations, the results of this study have the potential to significantly impact the medical and substance use services provided to YBLMSM and YBLTW in the United States by providing rigorous scientific evidence outlining approaches and strategies to improve uptake and engagement in HIV and prevention cascade. Despite accounting for disproportionate rates of HIV, most interventions in youth do not focus only on youth of color. This study focuses solely on youth of color in 3 urban cities. A major strength of the PUSH study is that it further provides information about the use of a multi-city approach to engage youth of color, along with exploring similarities and differences across locations. This work will provide data on the prevention, treatment, and sexual health trajectories of YBLMSM and YBLTW, including how to promote facilitators, address barriers to engaging in care, and end the HIV epidemic in this population.

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Conflicts of Interest

None declared.

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Abbreviations

ART: antiretroviral therapy
CHOP: Children's Hospital of Philadelphia
CRAFFT: car, relax, alone, forget, friends, and trouble
e-coupons: electronic coupons
eRDS: electronic respondent-driven sampling
FGDs: focus group discussions
GEE: generalized estimating equations
HPTN: HIV Prevention Trials Network
KI: key informant
KIIs: key informant interviews
LGBTQ: lesbian, gay, bisexual, transgender, queer
MEI: mobile-enhanced intervention
MI: motivational interviewing
MSM: men who have sex with men
NIDA: National Institutes of Drug Abuse
OR: odds ratio
PrEP: pre-exposure prophylaxis
PUSH: Providing Unique Support for Health
RCT: randomized controlled trial
RDS: respondent-driven sampling
SBIRT: screening, brief intervention, and referral to treatment
SOC: standard of care
SUDs: substance use disorders
TW: transgender women
YBLMSM: young Black and Latinx men who have sex with men
YBLTW: young Black and Latinx transgender women

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Protocol

A Mobile Social Network–Based Smoking Cessation Intervention for Chinese Male Smokers: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Approximately 2 million Chinese people die annually from tobacco-related diseases, mostly men; yet, fewer than 8% of Chinese smokers ever receive any smoking cessation advice or support. A social network–based gamified smoking cessation intervention (*SCAMPI: Smoking Cessation App for Chinese Male: Pilot Intervention*) is designed to help Chinese male smokers to quit smoking.

Objective: This paper aims to present the protocol of a study examining the preliminary effectiveness of SCAMPI by comparing the prolonged abstinence rate of a group of users with a comparator group during a 6-week follow-up period.

Methods: A two-arm pilot randomized controlled trial was conducted to assess the preliminary effectiveness and acceptability of the SCAMPI program as a smoking cessation intervention. After initial web-based screening, the first 80 eligible individuals who had gone through the required registration process were registered as participants of the trial. Participants were randomly allocated to the intervention group (n=40) and the control group (n=40). Participants in the intervention group used the full version of the SCAMPI program, which is a Chinese smoking cessation program developed based on the Behavior Change Wheel framework and relevant smoking cessation and design guidelines with involvement of target users. The program delivers a range of smoking cessation approaches, including helping users to make quitting plans, calculator to record quitting benefits, calendar to record progress, gamification to facilitate quitting, providing information about smoking harms, motivational messages to help users overcome urges, providing standardized tests to users for assessing their levels of nicotine dependence and lung health, and providing a platform to encourage social support between users. Participants in the control group used the restricted version of the SCAMPI program (*placebo app*).

Results: Recruitment for this project commenced in January 2019 and proceeded until March 2019. Follow-up data collection was commenced and completed by June 2019. The primary outcome measure of the study was the 30-day bio-verified smoking abstinence at the 6-week follow-up (self-reported data verified by the Nicotine Cotinine Saliva Test). The secondary outcome measures of the study included participants' cigarette consumption reduction (compared baseline daily cigarette consumption with end-of-trial daily cigarette consumption), participants' 7-day smoking abstinence at 4-week and 6-week follow-up (self-reported), participants' 30-day smoking abstinence at 6-week follow-up (self-reported data only), and participants' acceptability and satisfaction levels of using the SCAMPI program (measured by the Mobile App Rating Scale questionnaire).

Conclusions: If the SCAMPI program is shown to be preliminary effective, the study will be rolled out to be a future trial with a larger sample size and longer follow-up (6 months) to identify if it is an effective social network–based tool to support Chinese male smokers to quit smoking.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12618001089224; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=375381

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KEYWORDS

mHealth; mobile phone; smoking cessation; public health

Introduction

Burden of Tobacco Smoke

Every year, approximately 2 million Chinese people are killed by tobacco-caused diseases [1]. Still, nearly 300 million Chinese people continue to use tobacco each day [1]. Among these smokers, 95% are male [2]. Tobacco use caused 25% of Chinese male deaths [1]. In addition to health harm, tobacco use in China also leads to societal harm [1]. The economic cost of smoking in China amounts to ¥393 billion yuan (US $57.4 billion dollars) per year [1]. This includes direct costs related to health care expenditures and indirect costs related to lost productivity due to early mortality and morbidity [1].

According to the 2010 Global Adult Tobacco Survey in China, 36.4% of Chinese smokers had tried to quit in the past 12 months, whereas 91.8% of them had never received any smoking cessation services [3]. A survey in 2014 found that over half of Chinese smokers never received any quit smoking advice from their health professionals [4]. Since 2006, although some smoking cessation clinics had been set up and the National Quitline had launched, due to limited exposure and accessibility, they have rarely been used by Chinese smokers [5].

Mobile Smoking Cessation

A 2019 Cochrane review of mobile phone–based interventions for smoking cessation demonstrated the effectiveness of mobile technology in supporting smoking cessation [6]. The most recent World Health Organization report on the global tobacco epidemic indicated that personalized smoking cessation advice and support from mobile phone messages can be a cost-effective tool contributing to address the public health problem of tobacco use [7]. Mobile phone–based smoking cessation interventions have proven to be a cost-effective tool for supporting smokers to quit smoking. Some studies also showed that mobile smoking cessation apps can create short-term impacts on helping smokers to quit smoking [8-13]. A recent study has shown that daily smokers using a behavioral, decision-aid smartphone app achieved 23.8% self-reported 3-month continuous abstinence [14].

The 2017 Connected Consumer Survey conducted by Google Inc noted that 83% of Chinese people use smartphones [15]. China is regarded as the fastest growing smartphone market in the world, with a 10% increase in smartphone penetration rate in the past 5 years [16]. China has the largest smartphone user group (n>700 million people) in the world [17]. Among all the functions and apps of smartphones, WeChat is the most popular app (social network platform) in China. In 2020, 1.2 billion people were monthly active users of WeChat [18]. WeChat users are highly engaged with the app; nearly 80% of WeChat users use the app for >30 min daily [18]. WeChat has become a major tool in communication, entertainment, and payment for Chinese smartphone users.

Aim of the Study

As previously mentioned, Chinese males are the largest smoking population group in the world. Most Chinese smokers have limited access to smoking cessation services. The lack of appropriate smoking cessation services and limited accessibility to current smoking cessation support lead to a low smoking cessation success rate [19]. The high smartphone penetration rate and usage rate in China provide a great opportunity for developing and implementing smartphone app–based smoking cessation interventions. The potential for WeChat-based smoking cessation interventions to impact and reach out to millions of Chinese smokers is possible like never before.

The prevalence of cigarette smoking in Chinese males is substantial, and mobile smoking cessation programs hold much promise to provide cost-effective support to help smokers to quit. To date, there have been no reported investigations on the efficacy of delivering a smartphone social network–based smoking cessation intervention for Chinese male smokers via a social network platform.

The aim of this study is to introduce the SCAMPI program, which was designed to support Chinese male smokers to quit smoking and present the protocol of a pilot randomized controlled trial (RCT) that assesses the preliminary effectiveness of the SCAMPI program. The study examines the quit rates of abstaining users of the full version SCAMPI program versus the quit rates of a comparator group for a 6-week period. The pilot trial's main hypothesis is that users of the full version program will have higher biochemical verified 30-day smoking abstinence during the follow-up measures in comparison with the comparator group.

Methods

Study Design

This study will be a pilot, two-arm, parallel RCT. We will evaluate the preliminary effectiveness and acceptability of our SCAMPI program as well as recruitment and retention for estimating the sample size of a future definitive trial. All trial procedures will be conducted web-based via WeChat (Tencent). Ethical approval was granted by the University of Auckland Human Participants Ethics Committee (reference number: 021649) and the Zhejiang University School of Public Health Research Ethics Committee (reference number: ZGL201801-2).

Study Setting

The study setting of this pilot trial will be completely online via the social network platform WeChat. The SCAMPI program will not need to be downloaded or installed on participants' mobile phones, but they will be authorized to use the program via the WeChat platform.

Participants

Eligibility Criteria

Chinese male smokers will be eligible for inclusion in the study if they indicate at screening that they are smokers (both daily smokers *smoking any types of tobacco products on a daily basis* or occasional smokers *smoking any types of tobacco products occasionally [at least once in a week]*) aged between 25 and 44 years [5], have access to a smartphone, have a WeChat account, have adequate knowledge of Chinese language, and are willing to participate in the study and provide follow-up information at scheduled points of the study. People will be excluded from the sample if they report in the screening test that they are involved in any other types of smoking cessation interventions.

Recruitment

Online advertisement of the pilot trial will be delivered through WeChat to different WeChat users. Potential participants who read the trial advertisement and were interested in participating could subscribe to the SCAMPI WeChat official account (OA). Once they subscribe to the account, they will receive an auto-replied trial instruction. People can tap the registration link on the instruction to register as a participant of the study.

In the registration system, potential participants will be screened to ascertain their eligibility for the study. Eligible participants will be provided with the participant information sheet and consent form for them to read. After they complete reading the documents, they will be asked to provide electronic consent (e-consent) by tapping the *agree* button.

Within the e-consent, participants will then be directed to complete the baseline assessment. A participant will receive his first study compensation once he completes the registration to strengthen his relationship with the study.

Randomization and Allocation

Participants that fulfilled eligibility criteria and completed baseline assessment will be randomized in a 1:1 ratio to either an intervention group or a control group. The randomization sequence was generated by the trial statistician (YJ) using block randomization with variable block sizes of 2 or 4. The final randomization list was concealed in the database until the point of randomization.

Randomization will be performed upon completion of the baseline assessment. Each participant will have a unique code based on the sequence of completing the registration (participant no. 1 to no. 80). Randomization will be implemented based on the participant's code. Participants who are randomized into the intervention group will have access to the full version of the SCAMPI program. Participants who are randomized into the control group will have access to the restricted version of the SCAMPI program.

Intervention

The SCAMPI program was designed using the behavior change wheel (BCW) framework, a theory- and evidence-based tool for designing interventions based on an analysis of the nature of the behavior, the mechanisms that need to be changed to bring about behavior change, and the interventions and policies required to change those mechanisms [20]. It is considered as one of the most inclusive behavior change framework that was developed from 19 frameworks of behavior change identified in a systematic literature review [20].

The BCW framework starts with a theoretical understanding of behavior by the *capability, opportunity, and motivation to behavior model* (COM-B model) to determine what needs to change for the behavioral target to be achieved and what intervention functions are likely to be effective to bring about that change [20]. After selecting the intervention functions most likely to be effective in changing the smoking behavior of the target population, these will then be linked to specific behavior change techniques (BCTs), which will be codable to a mobile social network–based smoking cessation program [21,22]. The content, user interface (UI), and user experience (UX) design of the SCAMPI program were developed based on the China Clinical Smoking Cessation Guideline (CCSCG) [23] and WeChat mini-program design guidelines [24].

The application of the BCW framework for developing the SCAMPI program was under a process called collaborative product development (CPD), which is based on the principles of user-centered design (UCD) developed by Preece et al in 2004 [25]. In this study, UCD occurred in 2 forms: (1) consulting users about their needs of the proposed mobile health app–based smoking cessation intervention and (2) involving users as partners with researchers throughout the design and development process [25].

In the CPD stage, 20 potential end users (Chinese male smokers aged 25 to 44 years) were recruited through WeChat. These 20 participants provided their ideas about the desired components of a smoking cessation program through completing a development questionnaire (Multimedia Appendix 1). In the 1-month period, app development progressed and relevant questions were posted on SCAMPI OA to identify participants' preferences for the program's UX and UI design. At the end of the CPD period, participants' acceptability and satisfaction level toward the app were identified by completing an online questionnaire based on standard questions from the Mobile App Rating Scale (MARS) questionnaire (Multimedia Appendix 2) [26]. A total of 16 out of 20 participants completed the questionnaire, and the average rating of the SCAMPI program was 4.4 out of 5.0.

On the basis of the findings from participants' responses to the development questionnaire and the behavior analysis of the target population's smoking behavior [5,27], 11 key behavioral factors of the target population's smoking behavior were summarized. These 11 factors reflect the 5 main components of the COM-B model. By applying the BCW to navigate the

BCTs, 48 BCTs are relevant to these 5 reflected components of the COM-B model. Screening by the WeChat mini-program design guideline and the relevant context (eg, the program will be used by Chinese male smokers in China), 43 BCTs were considered as deliverable through the WeChat platform (Multimedia Appendix 3). Identified BCTs were integrated and coded as functions of the program. Table 1 shows the functions of the SCAMPI program and the corresponding BCTs that are aimed to be achieved by each function.

Table 1. Functions of the program and corresponding behavior change techniques codes.

Functions	Corresponding behavior change techniques
Design of the program	RD[a]1
Calculator, data capturing, and recoding	BS[b]6, BM[c]9, RC[d]8, RI[e]1, RI2, RI3, and RI4
Calendar	BM3
Content of the program	RC1, RC4, and RC7
Game	BM5, BS4, BS5, and BS6
Informational and practical tool	BM1, BM10, BS1, BS2, BS10, A[f]5, RC5, RC6, RC10, BM8, BS10, BS7, BS8, BS11, and RD2
Motivation	BM2
Other	Health testers, red packet (compensation)
Planning	BS3
Social support	A2

[a]RD: general aspects of the interaction (R) focusing on the delivery of the intervention (D).

[b]BS: specific focus on behavior (B) and maximizing self-regulatory capacity or skills (S).

[c]BM: specific focus on behavior (B) and addressing motivation (M).

[d]RC: general aspects of the interaction (R) focusing on general communication (C).

[e]RI: general aspects of the interaction (R) focusing on information gathering (I).

[f]A: promote adjuvant activities (A).

In summary, besides the design and content, the SCAMPI program has the following functions: (1) calculator to record quitting benefits (eg, money saved by not smoking), (2) calendar to record the progress of smoking cessation (eg, which date the users did not smoke), (3) gamification to facilitate quitting (eg, ranking board for showing users who make the longest continuous smoking abstinence), (4) providing information about smoking harms and health benefits from smoking cessation, (5) sending motivational messages (based on requests from users) to help users overcome urges, (6) providing standardized tests to users for assessing their levels of nicotine dependence and lung health, (7) helping users to make smoking cessation plans, and (8) providing a social support platform to users for delivering peer support between users. Screenshots and Quick Response (QR) codes of the SCAMPI program are provided in Multimedia Appendix 4.

As the target users of the program will be Chinese male smokers, all contents of the program were designed to be in Chinese. Table 2 presents examples of database content by themes (eg, smoking harms and quitting tips). The database content is based on the taxonomy of BCTs for smoking cessation via a text messaging intervention [22]. The program database includes a pool of 40 articles about smoking harms, all of which are coded to be sent to users on a daily basis through the SCAMPI OA. Each of these articles may take less than 3 min for participants to read. Articles are presented in the form of text and images. Participants will be prompted to read the articles, and they can decide when to read the articles and if they want to re-read the articles. All articles will be stored in SCAMPI OA throughout the trial and after the trial is completed. Participants in both groups and other subscribers to the SCAMPI OA will be able to have access to these articles freely after the completion of the trial. Information on the articles was referred to the CCSCG [23]. In addition, the program was designed according to the WeChat mini-program design guidelines [24]. The principles of friendliness and courtesy, clarity, convenience and elegance, and consistency have been used in the UX and UI design of the program.

Table 2. Examples of the program database content.

Themes	Examples of titles	Behavior change techniques
Smoking harms	“There are about 7,000 chemical components in tobacco, 69 of them are carcinogenic?!”	Provide information on consequences of behavior in general
Quitting tips	“When you feel urge to smoking, try deep breath and some physical exercise to distract your urge.”	Provide information on supporting behavior
Motivational messages	“Keep it up! You are XX days without smoking.”	Facilitate relapse prevention

Participants in the intervention group will have access to the full version of the SCAMPI program, and participants in the control group will have access to the restricted version of the SCAMPI program. Participants of the trial had free access to the SCAMPI program, both the full and the restricted versions. By the end of the trial, all WeChat users will have free access to the SCAMPI program. People can have access to the SCAMPI program by either search keywords "smoking or smoking cessation or SCAMPI" on the WeChat platform or scan the SCAMPI program QR codes.

The full version of the SCAMPI program has functions and content as described above. The restricted version of the program provides contact information of standard smoking cessation care (eg, Quitline in China and local smoking cessation clinics) to its users. Participants in both groups can use the corresponding versions of the SCAMPI program based on their willingness of when, where, and how long. The minimum frequency of using the program was once a week, to provide participants' daily cigarette smoking status throughout the week.

One investigator (JC) will have a minimum level of involvement in the trial, only if any of the following situations happen: (1) participants develop serious mental health issues by quitting smoking, investigator will terminate the participation immediately and refer the participants to health care providers; (2) participants want to withdraw from the trial, investigator will kindly ask the reasons for withdrawal only if participants are willing to answer; and (3) participants do not provide their smoking status for a week, friendly reminders will be sent by the investigator to remind participants to provide the data.

Prompts and messages of the program will only be triggered by requests from users (eg, motivational messages to support users from smoking urges or read program posts about information on smoking harms). The only message users receive will be to remind them to provide their smoking status; it will be triggered in the 48 hours after the date that users are requested to provide their daily smoking status of the week. The reminding messages will be delivered at a frequency of 3 times a day (once every 8 hours) for 2 days via WeChat message.

There will be no specific training session provided to the users. After successfully registering as participants in the study, participants will receive a message to introduce the versions of the program they are going to use in the trial. As the program was built natively on the WeChat platform by adapting the WeChat mini-program design guideline, WeChat users are expected to have no challenges in using any functions of the program.

Compensation

Participants in both groups will receive weekly WeChat messages to remind them to enter their daily cigarette consumption. The compensation for participation was delivered in a form called WeChat red packet (*Hongbao*). In Chinese culture, red packet is a monetary gift that is given during holidays or special occasions such as weddings, graduation, or the birth of a baby [28]. The red color of the envelope symbolizes good luck and is a symbol to ward off evil spirits [28]. The WeChat red packet is a widely used online currency in China and is transferrable through the WeChat platform [28]. Recipients of the WeChat red packet can use the value of the red packet to purchase goods or use services in China [29]. The WeChat red packet will be provided to participants as compensation to enter the data as requested. Participants from both intervention and control groups will receive the same reminding message and the same WeChat red packet. There is no specific incentive for a particular group to provide their smoking status.

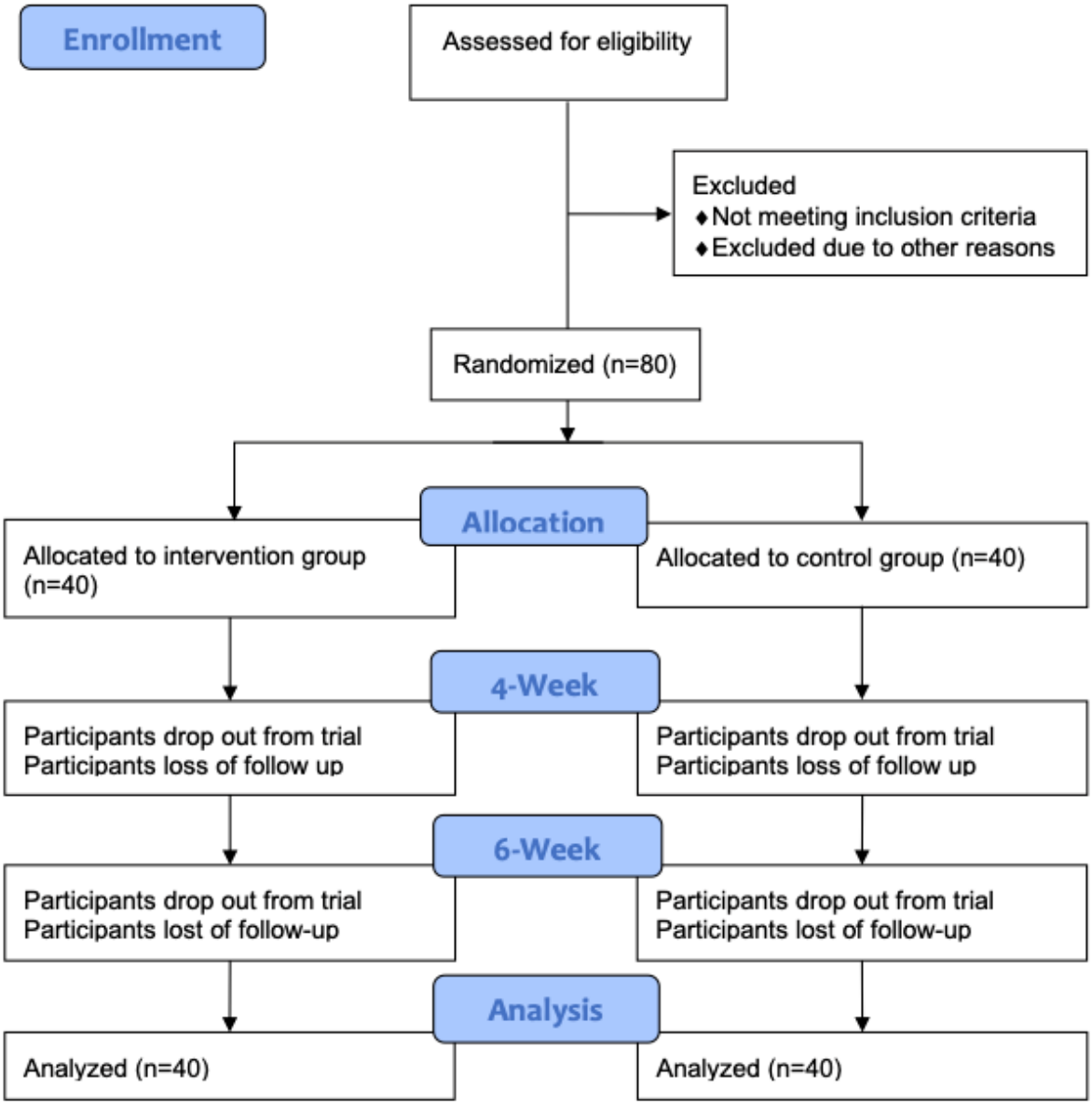
The compensation in this study will be given through 7 sessions (registration and 6 weekly data collection of cigarette consumption in the past week). Once participants complete each data entry session, the WeChat red packet pops out as compensation (participants in both groups receive the same WeChat red packet). The answers to the questionnaires had no impact on the value or form of the WeChat red packet participants (in both groups) received.

It has been proven that incentives may be able to give a useful improvement in reducing the quantity of missing data in trials [30-33]. A small financial incentive has minimal impact on the trial's results [34]. In this trial, the financial value of the WeChat red packet provided to each participant (both groups) was ¥35 RMB (approximately US $4.93), which is considered as a small financial incentive [34]. Meanwhile, compared with traditional methods of incentive delivery (eg, courier post and cash), the WeChat red packet is more secure and convenient. The WeChat red packet was only used as a method to maintain the completion of questionnaires and retention of the trial. Upon completion of the 6-week follow-up, the full version of the SCAMPI program will be offered to participants in the control group.

Procedures

The flow of participants' experience in the trial is presented in Figure 1. After providing informed consent, participants will be randomly allocated to different groups (intervention and control group, n=40 in each group). Participants randomized to the intervention group will have access for 6 weeks to the full version of the SCAMPI program, and participants randomized to the control group will have access for 6 weeks to the restricted version of the SCAMPI program. On completion of the 6-week follow-up assessment, participants in the control group will be offered free full access to the SCAMPI program. All data on program use were recorded until the end of the trial.

Figure 1. User experience in the trial.



All participation and procedures of the trial will be completed online through the WeChat platform. Participants who report themselves has 30-day continuous smoking abstinence at 6-week follow-up will receive a pack of cotinine test kit to test the nicotine levels of their saliva to biochemically verify their self-reported smoking abstinence.

Data of the trial will be collected online via the WeChat platform. Participants in both groups recorded their daily cigarette consumption for the week throughout the trial period. Usage data to the corresponding versions of the SCAMPI program were recorded by the server of the program. Participants' baseline data and satisfaction with the program (for participants in the intervention group only) were collected through electronic questionnaires (registration questionnaire and end-of-trial questionnaire).

The registration questionnaire asked participants about their demographics, smoking status, willingness to quit smoking, and so on (Multimedia Appendix 4). The registration questionnaire was developed based on a national online survey about smoking behaviors of Chinese smokers [5,27]. The end-of-trial questionnaire (Multimedia Appendix 5) was developed and shaped based on a standard questionnaire, the MARS questionnaire [26]. It focuses on assessing users' perception and satisfaction with the app or software or mobile program they used. Both questionnaires were overviewed and commended by experts from WeChat to ensure that their user experience met the Chinese users' preferences.

Retention

To prevent missing data, an effort will be made to retain the participants in the trial for the follow-up data collection. However, participants who withdraw their consent will discontinue their participation in the study. Participants who continue not entering their smoking status for 2 weeks will be considered as lost to follow-up. Participants who dropped out

of the trial or who were lost to follow-up were considered to be smoking.

The strategies for improving the adherence to the study include the following: (1) gentle WeChat messages reminder—a weekly message will be sent to participants in both groups to remind them to enter the data about their daily cigarette consumption of the week, (2) participants in both groups will receive a WeChat red packet after they enter the data as requested, and (3) a button for *feedback* is available to participants in both groups on the main page of the SCAMPI OA. Participants were prompted to use text or voice messages to make their feedback or report their usage difficulties. Instant guidance to support participants to use the program will be provided by the program.

Withdrawal Criteria

As part of the informed consent procedure and in accordance with best practice guidelines, the participant information and consent processes will clearly state that participation is voluntary, and participants will be free to withdraw at any stage of the research. Other reasons for withdrawal include the termination of the study for any reason.

As a mobile social network–based smoking cessation intervention, we believe that the intervention is barely harmful to any users. If a participant reports a severe physical or mental discomfort by using the SCAMPI program, the investigator (JC) will terminate their participation immediately and refer them to health care professionals. Events will be recorded and reported.

Results

Baseline Assessment

At the baseline assessment, the following data will be collected: age, marital status, employment status, family structure, age at smoking initiation, smoking cessation history, smoking status (consumption and frequency), and smoking cessation services usage history. These data will be collected at the beginning of the trial using an electronic questionnaire called the registration questionnaire (Multimedia Appendix 5).

Primary Outcome Measure

The primary outcome of this pilot trial will be the participants' biochemical verified 30-day smoking abstinence at 6-week follow-up. At the 6-week time point, researchers will review participants' (in both groups) self-reported smoking status in the past 30 days to identify their self-reported 30-day smoking abstinence. The 30-day smoking abstinence is usually used as the primary outcome measure for smoking cessation intervention trials recommended by the Society for Research on Nicotine and Tobacco [35]. Quit failure was defined as any cigarettes smoked in the past 30 consecutive days. This measurement is also known as the 10th level of smoking abstinence in the Chinese standard for smoking cessation [23].

At the 6-week time point, a nicotine cotinine saliva test kit will be sent to participants (in both groups) who report themselves with 30-day smoking abstinence to verify their smoking abstinence status. These participants will be requested to complete the test at home (clear instruction provided) and upload a photo or a short video of the strip test results to the SCAMPI OA. The cotinine test has proven to be a valid and reliable method to test saliva samples for verification of smoking status [36,37].

Secondary Outcome Measures

The secondary outcomes of the study included participants' tobacco consumption changes through the trial period, retention of the trial, program (both versions) usage, and users' satisfaction with the program (only for intervention group participants).

Tobacco consumption changes include measures of the following:

1. Participants' cigarette consumption reduction: Participants will be required to provide their daily cigarette consumption (as a categorial range such as "1 to 5 sticks cigarettes per day") at the baseline assessment. By using these data to compare with their daily smoking status through the pilot trial, researchers will be able to identify the reduction in cigarette consumption of participants (in both groups). Participants who reduce their consumption by at least one category (eg, from "16 to 20 sticks of cigarettes per day" to "10 to 15 cigarettes per day") from baseline will be counted as successfully achieving smoking reduction.
2. 7-day smoking abstinence at 4-week and 6-week follow-up: At the 4-week and 6-week time points, researchers reviewed and analyzed participants' (in both groups) smoking status in the past 7 days to identify their 7-day smoking abstinence at both these time points. A 7-day smoking abstinence is defined as not a single cigarette being smoked in the past 7 days [35].
3. 30-day self-reported smoking abstinence at 6-week follow-up: At the 6-week time point, researchers will review and analyze participants' smoking status in the past 30 days to identify their self-reported 30-day smoking abstinence. A 30-day smoking abstinence is defined as not a single cigarette being smoked in the past 30 days [35].

The retention rate of the trial refers to participants providing their daily smoking status at the end of every week.

Program usage will be measured by the number of times participants interact with the assigned versions of the SCAMPI program. At the end of the pilot trial, researchers will review the data on how many times participants like, comment, forward, post content from SCAMPI OA on a personal board, or have a conversation with their friend. The data on the number of times participants used the SCAMPI mini-program (for participants in the intervention group only) and the data on the number of times participants (in both groups) communicated with the program (by sending text messages, voice messages, or emoji) to the SCAMPI OA will also be collected and reviewed. These data may reflect the level of engagement between users in the SCAMPI program.

Users' satisfaction with the SCAMPI program will be measured by a standard MARS questionnaire at the end of the trial. As some questions on the questionnaire are not applicable to the restricted version of the program, only participants in the

intervention group will be requested to complete the questionnaire (Multimedia Appendix 6) [38,39].

Data Collection

All data of the study will be collected online through the social network platform WeChat. Table 3 shows the schedule of different data collections of the study.

Table 3. Schedule of study data collection.

Characteristics	Week 1 (day 0)	Week 1-5 (day 1-35)	Week 6 (day 36-42)
	Screening + baseline data collection + randomization	Follow-up data collection	Follow-up data collection
General data			
Eligibility	✓[a]	—[b]	—
Electronic consent	✓	—	—
Demographics	✓	—	—
Quitting history	✓	—	—
Smoking cessation interventions usage	✓	—	—
Primary outcome			
Participants' biochemical verified 30-day smoking abstinence at 6-week follow-up	—	✓	✓
Secondary outcomes			
Cigarette consumption	✓	✓	✓
7-day smoking abstinence at 4-week and 6-week follow-up	—	✓	✓
30-day self-reported smoking abstinence at 6-week follow-up	—	✓	✓
Participants' retention	✓	✓	✓
Program usage	—	✓	✓
Users' satisfaction with the program (intervention group)	—	—	✓

[a]Data were collected in the described timepoint.

[b]Data were not collected at the described timepoint.

Screening data will be collected at week 1 (day 0) via the registration questionnaire to determine eligibility for all individuals who read the study advertisement and entered the study registration system. The questionnaire consists of a short overview of the aim of the study and questions regarding the person's demographics, additions, quitting history, willingness to quit, and the usage of other smoking cessation interventions. All questionnaires of the trial were delivered by the Tencent Questionnaire platform, which is compatible to the WeChat platform.

Data on participants' cigarette consumption will be collected from day 1 to day 42 of the study via the same questionnaire platform. At the end of each week, participants will be provided with a link through WeChat messages to have access to the corresponding online questionnaire to enter their cigarette consumption status on each day of the week.

Users' satisfaction with the SCAMPI program (intervention group only) will be collected on day 42 along with the last weekly cigarette consumption status checking questionnaire. Data collected through online questionnaires will be downloaded from the platform and stored in a secure university server after every collection.

The program usage data (both versions) will be recorded by the WeChat mini-program and OA databases. These data will be exported and stored in the same place as data collected from online questionnaires.

On day 42, a link of ShunFeng courier WeChat mini-program will be sent to participants who self-reported themselves as 30-day smoking abstinence. Participants who received the link were requested to provide their address and recipient details to the courier through WeChat (none of these data were accessible or recorded by the research team). On the basis of the provided details, the kits with instructions will be sent to participants. Participants were requested to use the kit as instructed, take a photo or shoot a short video about how they used the kits and the relevant results (personal images were not asked), and send the test results to the SCAMPI OA.

Data Management

The National Institute for Health Innovation, University of Auckland, is responsible for storing and protecting the research data. As a digital trial, all data will be entered electronically.

All electronic data will be stored on the university computer with password protection. Only the principal investigator and members of the research team will have access to the computer-based data. All participants will be assigned a specific code number to protect their confidentiality. All data will be under the unique code number and stored for a period of 3 years after completion of the study.

Statistical Methods

Data from this study will be exported from different databases, the WeChat mini-program and OA databases for the data related to the SCAMPI program usage and the Tencent Questionnaire database for the data related to participants' demographics, additions, quitting history, willingness to quit, the usage of other smoking cessation interventions, and cigarette consumption during the study.

Baseline data collected from all participants will be summarized and presented. Continuous variables (eg, age) will be presented as numbers observed, means, and standard deviations. Categorical variables (eg, marital status) will be presented as frequencies and percentages. As any differences between randomized groups at baseline could only have occurred by chance, no formal significance testing will be conducted. Primary and secondary outcomes will be summarized descriptively at the identified time points. A generalized linear mixed model will be used to assess the effect of the SCAMPI program on participants' smoking cessation outcomes.

Power

We determined the power for the proposed main trial of this study. A total sample size of 530 (265 per group) will have 90% power at 5% significance (two-sided) to detect an absolute difference of 10% on the primary outcome between the 2 groups, assuming a control rate of 6.7% [19] and 20% loss to follow-up. Given the budget and resource limitations, in this study, we aim to recruit around (80/530, 15.1%) of the total sample size required for the main trial, that is, n=80 (40 per group), using an open recruitment strategy to recruit all participants within a month. At the end of the study, we will re-estimate the power of the final percentage differences between groups in the effectiveness report to further determine the exact final sample size of a full trial. The sample size is considered as a major limitation of the study.

Ethics Approvals

Ethics approval (reference number: 021649) was obtained from the University of Auckland Human Participants Ethics Committee. As this study targets Chinese male smokers, ethics approval (reference number: ZGL201801-2) was obtained from the Zhejiang University School of Public Health Research Ethics Committee.

Consent

All eligible individuals are given an electronic copy of the information sheet and informed consent form to read via WeChat. The information sheet provides a summary of the study, and the informed consent document states what the individual is about to participate in, the individual's rights as a research participant, and information about confidentiality. Individuals are encouraged to communicate with researchers through SCAMPI OA if they need any further explanation or information about the study. If the person chooses to participate in the study, that person will be asked to tap the *agree* button on the informed consent page of the registration questionnaire (Multimedia Appendix 5). Subjects who refuse to participate or who withdraw from the study were treated without prejudice. The reason for refusal or withdrawal will be noted if reported.

Confidentiality

All study-related data will be exported and stored securely at the university server under a coded identification number to maintain participant confidentiality. All data that contain personal identifiers, such as screening data for eligibility and informed consent forms, will be stored separately from study records identified by a code number. All local databases were secured with a password-protected access system. All data of the study were collected and stored electronically.

Discussion

Principal Findings

This pilot trial and its findings will contribute to the evidence available to inform the development and implementation of the SCAMPI program as a mobile social network–based smoking cessation tool. The primary outcome of the study was to contribute to an understanding of the preliminary effectiveness of the SCAMPI program as a smoking cessation intervention for the target population. The overall implementation of the study can have an impact on delivering smoking cessation interventions through social network platforms such as WeChat. The use of the SCAMPI program is not restricted to any specific place, time, or situation, and it is free to use. It can also contribute to the reduction of health care costs. In addition, the study will contribute significantly to future research on social network–based health intervention development and evaluation. It may provide new ideas about applying social network platforms to improve recruitment efficiency and engagement in public health research projects. The relatively small sample size and short-term follow-up due to time and budget limitations are common with mobile smoking cessation trials [40], which is a threat to the quality of the trial.

Trial Status

Recruitment for this project commenced in January 2019 and was completed in the same month. Follow-up data collection commenced and was completed by the end of June 2019.

Authors' Contributions

CB contributed to the concept development, study design, article writing, and reviewing. EH provided cultural insights for intervention development, article writing, and reviewing. YJ contributed to the study design, statistical plan, article writing, and reviewing. RW provided consultancy on the product concept development and development process guidance. TY provided consultancy on the product's cultural adaptation and the trial's Chinese ethics application. JC contributed to the literature search, technical and conceptual development of the SCAMPI program, study design, and article writing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Development Questionnaire.
[DOCX File , 19 KB - resprot_v9i9e18071_app1.docx]

Multimedia Appendix 2
Usability Testing Questionnaire.
[DOCX File , 17 KB - resprot_v9i9e18071_app2.docx]

Multimedia Appendix 3
Transition from behavioral factors to behavior change techniques.
[DOCX File , 23 KB - resprot_v9i9e18071_app3.docx]

Multimedia Appendix 4
Screenshots and Quick Response codes of the program.
[DOCX File , 1446 KB - resprot_v9i9e18071_app4.docx]

Multimedia Appendix 5
Registration Questionnaire.
[DOCX File , 21 KB - resprot_v9i9e18071_app5.docx]

Multimedia Appendix 6
End-of-trial Questionnaire.
[DOCX File , 17 KB - resprot_v9i9e18071_app6.docx]

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Abbreviations

BCT: behavior change techniques
BCW: behavior change wheel
CCSCG: China Clinical Smoking Cessation Guideline
COM-B: capability, opportunity, and motivation to behavior
CPD: collaborative product development
MARS: Mobile App Rating Scale
OA: official account
QR: Quick Response
RCT: randomized controlled trial
UCD: user-centered design
UI: user interface
UX: user experience

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Protocol

School-Based Multicomponent Intervention to Promote Physical Activity and Reduce Sedentary Time of Disadvantaged Children Aged 6-10 Years: Protocol for a Randomized Controlled Trial

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Abstract

Background: In our modern society, physical activity (PA) is decreasing and sedentary time (ST) is increasing, especially for children from disadvantaged neighborhoods. School-based interventions to promote PA and decrease ST are therefore required among this population in order to change children's lifestyle habits. Moreover, attentional capacities and academic achievement can be enhanced by chronic PA during childhood. The relationships between these variables have been poorly studied with this population.

Objective: The objective of this study is to present the rationale and methods for a randomized controlled trial among 6-10-year-old children with low socioeconomic status that will (1) evaluate the effectiveness of a school-based intervention designed to promote PA and reduce ST and (2) study the relationships between PA, ST, motor skills, attentional capacities, and academic achievement.

Methods: A randomized controlled trial was conducted in 2 eligible primary schools. During academic year 2016-2017, 1 school was randomly assigned as the experiment one and the other was assigned as the control one. Five assessments times were used: baseline (T1 [November 2016] to T2 [June 2017]), follow-up (T3 [November 2017] to T4 [June 2018]), and final assessment (T5 [June 2019]). The school-based intervention included various components on different levels of the socioecological model: (1) curriculum-based program for children; (2) sensitization workshops and newsletters for parents; (3) training workshops for teachers; (4) environmental adaptation of playgrounds and reorganization of recess time; (5) time adaptation of lunch breaks; and (6) collaboration with political groups. PA, ST, motor skills, and attentional capacities were evaluated and academic achievement was recorded.

Results: The presented intervention and its different assessments have been successfully implemented. In order to achieve the 2 objectives of this randomized controlled trial, data analyses are about to be completed.

Conclusions: The implementation of this randomized controlled trial can help to determine effective strategies to promote PA in the context of increasing prevalence of physical inactivity among children with sedentary lifestyle which will be useful for researchers, stakeholders, and public policy makers.

Trial Registration: ClinicalTrials.gov NCT03983447; https://clinicaltrials.gov/ct2/show/NCT03983447

International Registered Report Identifier (IRRID): RR1-10.2196/17815

(JMIR Res Protoc 2020;9(9):e17815) doi:10.2196/17815

KEYWORDS

children; school; intervention; promotion; physical activity; sedentary time; attention; academic achievement

Introduction

Background

Physical inactivity has been recognized in the last decade as a major cause of noncommunicable disease, being held responsible for more than 5.3 million of the 57 million deaths that occurred worldwide in 2008, and for a decrease in life expectancy [1]. Furthermore, physical activity (PA) has a protective effect against more than 20 chronic diseases, including obesity [2]. Thus, the World Health Organization (WHO) has set a global action plan to increase PA levels and decrease sedentary time (ST), with the aim of "a 15% relative reduction in the global prevalence of physical inactivity in adults and in adolescents by 2030" [3]. To reach that goal, primary school children are an important target because behaviors adopted in childhood affect health habits and lifestyle choices in adulthood [4,5]. International guidelines for 6-11-year-old children recommend at least 60 minutes of moderate-to-vigorous PA (MVPA) per day as well as a reduction of sedentary behavior [3]. However, data suggest that when conservative cut points are used to define MVPA, less than half of the children meet the 60-minute MVPA recommendation [6,7]. As an example, the IDEFICS study reported an average MVPA of 49 minutes for boys and 36 minutes for girls and an average ST of 370 minutes in 8-year-old children from 8 European countries [8]. Furthermore, children of low socioeconomic status seem to have lower PA levels as well as higher ST [9]. Thus, they should be specific targets for intervention because the WHO defines the reduction of inequalities as one of its Sustainable Development Goals [3].

Many studies have investigated the effectiveness of intervention programs for children to promote PA [10-12]. Given the fact that children spend a large part of the day at school, most of the interventions are carried out in this context [11-13]. This environment, dedicated to learning, allows the use of several actions and makes it possible to include children of any social class. Some interventions increase the frequency and duration of physical education classes and include health education workshops [14,15]. These workshops usually contain information on PA and nutrition. The results of these interventions are inconclusive because the children practice less PA outside of these extra physical education classes, leading to a reduced effectiveness [16,17]. In fact, school is not the only place for children to be physically active. The socioecological model of Sallis applied to health behavior identifies different levels of factors that influence children's behavior, ranging from personal, interindividual (family or friends), community and environmental, and societal levels [18,19]. Some interventions act only on environmental factors, such as a new playground design adapted to PA practice. This type of environmental adaptation increased light PA and decreased ST, but did not affect MVPA [20]. Thus, as underlined recently by the WHO, a system-based approach should be favored, which means that interventions have to be integrated and multilevel to actually increase levels of PA and decrease ST [3]. In fact, there is strong evidence for the efficiency of school-based interventions with family and community involvement and multilevel interventions [16]. Thus, if actions are implemented at schools, workshops for parents and teachers should be added, especially in disadvantaged neighborhood that include many children from low socioeconomic status families [16,17].

As stated by the WHO, if PA has to be increased, ST also has to be reduced, and healthy PA habits should be learned during childhood [3-5]. In fact, if 7-year-old children spend about half of their waking time in sedentary behavior, this proportion increases up to around 75% at 15 years of age [21]. Furthermore, the effects of physical inactivity and sedentary lifestyle are independent of health, especially at the cardiometabolic level [22]. Thus, specific interventions to reduce ST are needed. Usually, these interventions focus on the development of classroom material. A literature review analyzed 13 studies and showed that height-adjustable desks decreased sitting time in the classroom [23]. Active classroom lessons are also used in several intervention programs to promote PA and break down ST, leading to improvement in on-task behavior during academic instruction [24]. In order to show evidence of the hypothesized change of behavior, an objective method of measurement of PA and ST, such as accelerometry, in preintervention and postintervention periods is necessary because self-reported ST is highly underestimated [25].

To help convince the educational authorities as well as the teachers to implement such interventions, recent evidence underlines the role of physical movement in the establishment of fundamental mental processes during childhood and adolescence, leading to cognitive benefits [26,27]. PA seems to have positive effects on the attentional capacities of children as well as academic achievement [28]. In fact, physical condition would be a mediatory element between PA and executive functions that include attentional capacities [29]. In addition, the development of gross and fine motor skills has a positive impact on cognitive capacities [30]. Thus, it is necessary to explore the relationships between PA, motors skills, attentional capacities, and academic achievement for children with low socioeconomic status.

Aims

This article aims to present the rationale and methods for a randomized controlled trial among 6-10-year-old children with low socioeconomic status that will (1) evaluate the effectiveness of a school-based intervention designed to promote PA and reduce ST and (2) study the relationships between PA, ST, motor skills, attentional capacities, and academic achievement.

Methods

Context

In 2016, a Pyrenean cross-cultural structure called Centre for the Promotion of Physical Activity and Health (CAPAS-City) was created to promote PA in 2 cities (Huesca [Spain] and Tarbes [France]). It involves 4 partners: the city councils of Huesca (Spain) and Tarbes (France), and 2 research groups from the University of Zaragoza (Spain) and the University of Pau and Pays de l'Adour (France), respectively. CAPAS-City was funded by the European Regional Development Fund (FEDER) programme for territorial cooperation and sustainable development of cross-border regions (Spain, France, and

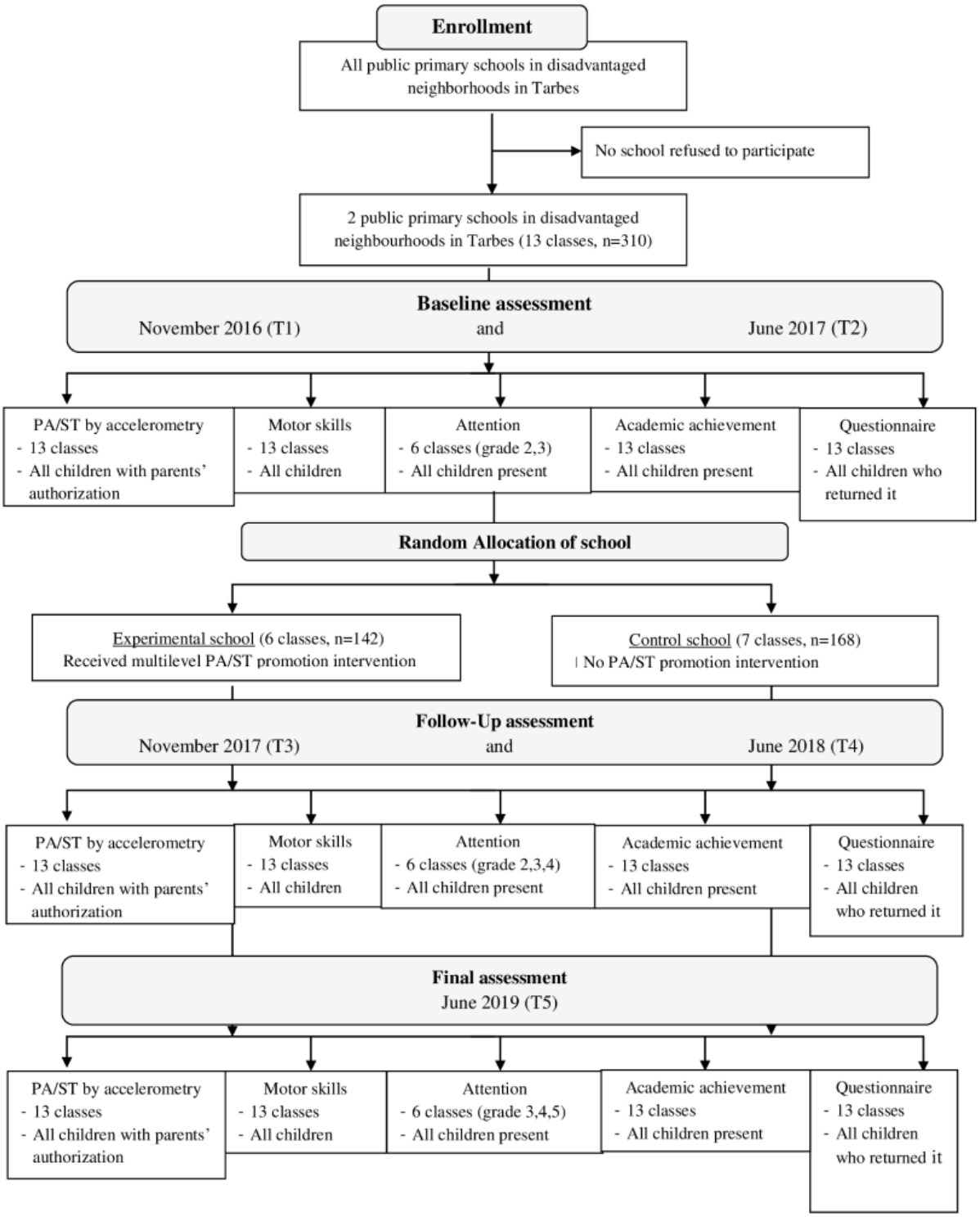
Andorra in this case) called POCTEFA 2014-2020 (EFA095/15). This center is in charge of developing PA programs and promotional activities that have a beneficial impact on health especially in disadvantaged populations that are more prone to health issues. It is within this framework that this study has been conducted because it is focused on children from disadvantaged neighborhoods.

Study Design and Population

The study was designed as a randomized controlled trial with 2 arms. In a mid-sized city in the southern part of France, 2 primary schools located in the city's disadvantaged neighborhood were invited to participate in the study. In France, neighborhoods are classified as disadvantaged on the criterion of income per inhabitant: this income is compared with the average income of the city and that of France. This defines the unfavorable social and economic conditions of the neighborhood and its inhabitants. For example, in the neighborhood considered in this study, the unemployment rate is the highest in the city (26% vs 18%) as well as the prevalence of social housing (49% vs 23%).

Both primary schools agreed to participate in the project. They included children from grade 1 (6 years old) to grade 5 (10 years old) and had never benefited from any intervention in the field of PA. Schools were randomly assigned to either experimental (School A) or control group (School B; see Figure 1). Because the intervention is school based, all the children were included in the study (n=141 for school A and n=148 for school B). Based on studies already published on the same theme, the effects of the intervention are expected to be moderate (standard difference≈0.32, equivalent to an average change in MVPA measurement of 8 minutes per day; SD 18 minutes). In addition, in order to detect a difference of 0.32 with a statistical power of 0.8, a significance level of .05, and a retention rate of approximately 91% with a pre/post comparison, the number of participants should be 70. As a precaution, more children were included. Thus, the number of children enrolled was above the minimum required.

Figure 1. Flowchart of participants. PA: physical activity; ST: sedentary time.



During the academic year 2016/2017, the following baseline assessments were carried out in these 2 schools: measurements of PA and ST, motors skills, attentional capacities, and academic achievement as well as questionnaires completed by parents. These assessments were carried out in November/December 2016 (T1) and May/June 2017 (T2). Children in both schools had to have parental permission to wear the accelerometer for PA and ST measurement. Motor skills were assessed for all the children at school and their records of academic achievement were collected. The measurements of attentional capacities involved only children in grades 2 and 3.

During the academic school year 2017/2018, the experimental school benefited from a school-based multilevel intervention to increase PA, reduce ST, and make children, parents and teachers aware of the importance of PA for health. This intervention program involved all the children from grade 1 to grade 5. During this interventional year, the same periods of assessment as those carried out at baseline were repeated in November/December 2017 (T3) and May/June 2018 (T4). A final assessment was carried out in June 2019 (T5) after 1 year without any special intervention in the experimental school.

Baseline and Follow-Up Assessments

Table 1 reports the number and percentage of children who participated in the assessment times (T1–T2–T3–T4–T5) in the experimental school (School A) and in the control school (School B).

Table 1. Children's participation in baseline, follow-up, and final assessments in the 2 schools.

Measurements	T1	T2	T3	T4	T5
School A					
Accelerometry, n/N (%)	91/142 (64.1)	96/142 (67.6)	74/135 (54.8)	45/137 (32.8)	71/134 (53.0)
Attention, n/N (%)	48/142 (33.8)	49/142 (34.5)	44/135 (32.6)	47/137 (34.3)	53/134 (39.5)
Motor Skills, n/N (%)	130/142 (91.5)	129/142 (90.8)	125/135 (92.6)	110/137 (80.3)	109/134 (81.3)
Academic Achievement, n/N (%)	118/142 (83.1)	118/142 (83.1)	105/135 (77.8)	105/137 (76.6)	95/134 (70.9)
Questionnaire, n/N (%)	90/142 (63.4)	90/142 (63.4)	60/135 (44.4)	60/137 (43.8)	58/134 (43.3)
School B					
Accelerometry, n/N (%)	121/168 (72.0)	116/168 (69.0)	90/154 (58.4)	51/154 (33.1)	86/175 (49.1)
Attention, n/N (%)	65/168 (38.7)	66/168 (39.3)	58/154 (37.7)	56/154 (36.4)	71/175 (40.6)
Motor Skills, n/N (%)	152/168 (90.5)	153/168 (91.1)	153/154 (99.4)	153/154 (99.4)	158/175 (90.3)
Academic Achievement, n/N (%)	156/168 (92.9)	156/168 (92.9)	140/154 (90.9)	140/154 (90.9)	99/175 (56.6)
Questionnaire, n/N (%)	113/168 (67.3)	113/168 (67.3)	73/154 (47.4)	73/154 (47.4)	57/175 (32.6)

Physical Activity and Sedentary Time

GT3X Accelerometers (ActiLife) were used as a valid objective measure to assess the levels of PA and ST [31-33]. These assessments were performed in T1, T2, T3, T4, and T5. Children wore the accelerometer on the right side of the hip, adjusted with an elastic belt, from morning to evening for 8 consecutive days. They removed it to sleep, during the shower, and for aquatic activities. The first day was excluded from the analysis and the data collection was carried out over 5 weekdays and 2 weekend days. The accelerometer had to be worn for at least 10 hours on weekdays and 8 hours on weekend days to be included in the analysis, according to the optimal methodological approach for accelerometry [34]. In addition, if the accelerometer detected at least 10 minutes of activity of 0 counts (cts), allowing this quota of time 1-2 minutes between 0 and 100 cts, this time was determined as "no wear time." To be considered as representative of children's usual behavior, wear time had to be valid for at least 3 weekdays and 1 weekend day [35].

For the treatment of accelerometer data, ActiLife version 6.13.3 software (ActiGraph) was used. In order to measure children's PA, which is described as spontaneous, it is preferable to use epochs of less than 15 seconds which makes it possible to detect more accurately the changes in the child's PA intensities [36]. Thus, we used 1-second epochs and 5 cut points to establish the different intensity categories [31,37]: sitting time 0-99 cts, standing time 99-300 cts, light PA 301-2295 cts, moderate PA 2296-4011 cts, and vigorous PA 4012 cts and more. To obtain ST, the first 2 cut points were added, and thus the cut point corresponding to ST was 0-300 cts.

In order to better understand the behavioral changes, PA and ST were analyzed within specific periods of the day corresponding to the French cultural children's schedule: time before school (08:00-08:30); morning and afternoon school time (08:30-12:00 and 14:00-16:00); lunch time (12:00-14:00); after-school time (16:00-19:00); evening time (19:00-21:00). During each of these periods, to be valid, the accelerometers had to be worn for 80% of the standard segment time, with this standard segment time being defined as the length of time in which at least 70% of the participants wore the monitor [31].

Motor Skills

Global motor skills were evaluated with 3 tests issued from the Eurofit Test Battery [38,39] because it is valid and reproducible for school children aged 6-18 [40]. They were implemented as described in the Eurofit Handbook [38]. Cardiorespiratory fitness was also measured with the PREFIT 20-m Shuttle Run Test, an adaptation of the original 20-m Shuttle Run Test for children [41]. These tests were carried out at T1, T2, T3, T4, and T5.

Standing Broad Jump

This test is included in the Eurofit Test Battery and measures the explosive power of the legs and intersegmental coordination [38].

Platte Tapping Test

This test is included in the Eurofit Test Battery [38]. It measures the speed and coordination of the upper limb.

6 × 5-m Shuttle Run

This test was adapted from the 10 × 5-m Shuttle Test of the Eurofit Test Battery [38]. It measures running speed and agility.

Cardiorespiratory Fitness: PREFIT 20-m Shuttle Run Test

The aerobic capacity was measured with an adapted version of the original 20-m Shuttle Run Test [42]: the PREFIT 20-m Shuttle Run Test, more appropriate for young children [41]. Children had to run back and forth between 2 lines 20 m apart with an audio signal giving the rhythm of the corresponding speed. The running speed increased by 0.5 km/h each minute.

Some adaptations of the original test were made to fit children's capacities by decreasing the initial speed (ie, 6.5 km/h instead of the original 8.5 km/h) and by having 2 evaluators running with a reduced group of children (eg, 8-12 of the same age) in order to provide an adequate pace. The test ended when the child failed to reach the end lines concurrent with the audio signal on 2 consecutive occasions or when the child stopped because of exhaustion. The results were expressed as the number of laps completed. From this value, the maximal aerobic shuttle running speed (km/h) and the maximal oxygen uptake (VO_{2max} mL/kg/min) can be calculated.

Attentional Capacities

The computer-based modified Erickson Flanker Task was used as a variant version of the Flanker-Task [43,44]. It was designed with the software SuperLab 4.5 (Cedrus Corporation). It permits the measurement of inhibition and cognitive flexibility, which are identified as attentional capacities [45]. Inhibition refers to focusing on essential elements of the environment while not focusing on disturbing elements, and cognitive flexibility involves changing from one cognitive operation to another. The sustained attention was evaluated as well. The task was to respond to a target stimulus while ignoring distracting stimuli presented on a 15-in. computer screen. In this version the stimuli were pictograms of a fish oriented either toward the left or toward the right. The child was instructed to press on the "P" key of the keyboard (located on the right hand side) with the right hand for target fishes facing to the right, and on the "A" key of the keyboard (located on the left hand side) with the left hand for target fishes facing to the left. The test included 3 conditions: (1) standard flanker, (2) reverse flanker, and (3) mixed condition. In the standard flanker condition, the fishes were blue. The target stimulus was the fish located in the middle of the screen. It could be oriented to the left or to the right and could be accompanied on either side by other fishes facing either direction and they had to be ignored (ie, distractors). In the reverse flanker condition, the fishes were pink. In contrast to the previous condition, the target stimuli were the fishes located on either side of the screen while the middle fish had to be ignored (ie, the distractor). These 2 conditions require sustained attention to remember the initial instruction and stay focused throughout the test, and inhibition of the appropriate distractor. In the mixed condition, trials from the standard condition (with blue fishes) and trials from the reverse condition (with pink fishes) were randomly mixed up. The child had to adapt to the variation of the rule to be applied. Thus, this condition required cognitive flexibility on top of sustained attention and inhibition.

For each condition, after being instructed in the task, the child practiced with 2 familiarization blocks of 7 stimuli: 1 block with feedback on the correctness of his/her answer and 1 block without feedback. If necessary, these blocks were repeated until it was made sure that the task was clearly understood. The child was asked to respond as quickly and as accurately as possible by pressing on the appropriate key ("P" or "A") according to the stimulus [44].

The reaction time and the correctness of the answers were recorded to measure sustained attention, inhibition, and flexibility. This test was carried out at each measurement period (T1, T2, T3, T4, and T5), only for children in grades 2, 3, and 4. Children were assessed during school morning from 8:30 to 12:00. The measurements took place in a separate classroom and 1-4 children were assessed at the same time. Each child was placed in a corner of the classroom in front of a 15-in. screen, with the attendance of 1 specialist researcher. The instructions were given verbally and individually by the specialist.

Academic Achievement

Measures of academic achievement for each child and for both schools were collected at the beginning of each academic year, that is, at baseline (T1), follow-up assessment (T3), and final assessment (T5). Criteria of assessment of the academic achievement were the same for both schools. These data were provided by the local educational services. Percentages of success for "reading," "spelling," "arithmetic," and "mathematics" were collected.

Questionnaire

In addition to collecting academic achievement data, a questionnaire was distributed at the beginning of each school academic year (ie, T1, T3, and T5). Parents were asked to complete a questionnaire in order to obtain (1) sociodemographic information (age and gender of the child, socioeconomic data measured by the 4-item scale "Family Affluence Scale II" [FAS II] [46], marital status, and level of qualification of the parents) and (2) subjective information related to children's PA and ST behavior (number of sports and outdoor activities practiced, parental perception of the competence of their children in PA practice, sedentary behavior of the child [time spent playing video games, watching television, and artistic and musical activities]).

Statistical Analysis

STATISTICA version 12.5 (StatSoft/Dell) for Windows and R software will be used. Descriptive statistics of MVPA and ST for the whole day and within the different specific periods of the day will be calculated for both schools at the different assessment times. To examine the effectiveness of the intervention to promote PA and reduce ST, ANOVAs contrasting 2 schools × 5 assessment times with repeated measurement on the last factor will be used on MVPA and ST. Furthermore, chi-square analysis will be carried out to compare the number of children between experimental and control groups who comply with MVPA recommendations for the overall day and during school time.

To explore the longitudinal relationship between PA, motor skills, attention, and academic achievement, multiple regression analyses will be conducted to determine which variables will predict academic achievement scores [47]. We will attempt to examine whether PA or motor variables predict academic achievement through attention. As there are many variables in each category, a principal component analysis will be used to select the variables that are most correlated. Finally, the decision tree process will be used to examine more accurately the longitudinal relationships between the variables selected.

Intervention Program

Because interventions that are integrated and multileveled seem to be more effective in triggering behavioral changes concerning the levels of PA and ST, this program has been conceived as a school-based approach with interventions at different levels of factors that influence children's behaviors [3,18,19]. More specifically, it is directed to the children (intrapersonal level), but also to their teachers and parents (interindividual level) and to their environment (physical and organizational levels). Furthermore, to be integrated, it has to be adapted to the real needs of the particular population to which it is dedicated. Thus, PA and ST data from the baseline assessment were analyzed to tune and adapt the intervention program.

Principal Outcomes From Measurements at Baseline Concerning PA and ST

On average, children aged 8-10 spent 67.20 (SD 17.83) minutes in MVPA and 602.97 (SD 36.32) minutes in ST on weekdays. At different periods of the school day, it appeared that (1) during school time, the international recommendation to spend 30 minutes in MVPA were fulfilled by only 26.92% of the grade 2 children and 5.40% of the grade 5 children. In fact, children spent 22-27 minutes in MVPA during school time while they were sedentary for 260-270 minutes. Thus, it was confirmed that school is a highly sedentary place where PA has to be promoted during recess and also during class time through sedentary breaks and active learning strategies. (2) During lunch time, sedentary activities represented 80% of the period (ie, 88-93 minutes of ST against 10-13 minutes of MVPA), suggesting that this period of the school day could be used for children to be more active and less sedentary through an organizational process. (3) Before school, only 2-3 minutes were spent in MVPA while 22 minutes were ST, suggesting that active transportation to school was scarce or that school is very close to home for some children. Thus, children's and parents' sensitization to active transportation should be developed.

PA and ST Intervention Program

According to the socioecological model and to the analyses of PA and ST at baseline, specific intervention actions have been carried out at the different levels of the model. Their content and objectives are detailed in Table 2.

The timings of these actions were coordinated across the different levels of the model. Thus, the contents of the different workshops for the children and the parents were coordinated with the training for the teachers. For example, workshops 1-3 for children took place at the same time of year as sensitization workshops 1 and 2 for parents and training workshop 1 for teachers in order to allow children to discuss and exchange views on these subjects ("what is PA?", "what is ST?") with the adults around them and for the teachers to reactivate part of the knowledge when they had the opportunity. Then, feedback from the baseline assessment of PA and ST levels and motor skills was given to the children, parents, and teachers. This was coordinated with workshops 5 and 6 for the children. This led to actions, learning, and discussions with the different actors (ie, children, parents, and teachers) in order to increase PA and decrease ST. Thus, around that time of year, children explored and tested concrete "activities in the schoolyard," parents came to sensitization workshop 3 (How can I influence my child's PA?), and teachers were trained in active classroom and sedentary breaks (training workshop 2). This training was followed by a demonstration of these activities in the class (Active classroom and sedentary breaks). Furthermore, during training workshops 3 and 4, teachers discussed strategies to increase children's PA and the different factors that can influence it. In parallel, some environmental adaptations were carried out. As noted earlier, the baseline assessment led the research team to realize that lunch time was highly sedentary (80% [~95 minutes] of the 120 minutes lunch) when it should be devoted to some active leisure. Therefore, discussions were held with the different staff working in the canteen to reorganize this time so that children spent less time sitting and more time playing and moving (Organizational modification of lunch break). In parallel, a discussion was carried out with the teachers to optimize the organization of the different areas of the schoolyard based on the games to allow children to find their favorite activity and then be more active (Organizational modification of recess games).

Around the middle of the school year, delineations of games in the schoolyard were created by the education department of the town hall (physical and material modifications of the schoolyard), following a participatory bottom-up approach. In fact, the first ideas came from the children (workshop 4: each child drew what he wanted to have in his schoolyard) and then a first selection was done at the class level (design of the schoolyard from the different individual suggestions). Finally, a consultation between the teachers, the research team, and the representatives of the town hall led to the final choices. Furthermore, discussions were carried out on the role of the surrounding environment in facilitating or preventing PA practice at the children's level with the "photovoice workshop," as well as at parents' level (sensitization workshop 4) and at teachers' level (training workshop 4).

To conclude the intervention, assessments were made with children (workshop 7), parents (sensitization workshop 5), and teachers (training workshop 5) to discuss the behavioral changes that took place and the strategies that were put into place (what worked well or what didn't?). A drawing contest was organized among children (workshop 8): they were asked to draw themselves in an active situation, and their drawings were presented to the education community and the parents at the end of the school year.

Finally, different political levels were involved during the intervention, such as the different services of the city town hall and the French national education system, which allowed the research team to conduct its actions.

Table 2. The different axes of the intervention: content and objectives.

Theme of each action according to the level of the socioecological level	Content
Intraindividual (level 1): children	
Workshop 1: “What is PA?”	Information about PA was given: the different intensities, the principal differences between PA and sport, and the benefits of PA on health.
Workshop 2: “How to practice PA?”	Different activities were presented to the child to be more active at school, in his/her neighborhood, in a sports club, and at different moments of the day.
Workshop 3: “What are sedentary habits?”	Information about the different sedentary behaviors that children can have in a day was given, as well as the effect of cumulative ST on health. The possibilities to decrease ST at each time of the day were analyzed.
Workshop 4: “What would you like to draw on the schoolyard to play, run, and have fun?”	Children had to draw schoolyard equipment and materials that they would like to have, to allow them to have fun and to move around. These proposals were then studied in each class, classified, and selected to make a proposal per class.
Workshop 5: “How does the accelerometer measure PA and ST?”	The mechanical operation of the accelerometer was studied. The data from the accelerometer were analyzed. The children determined their compliance with the WHO guidelines.
Workshop 6: “Do I practice enough PA every day to be healthy?”	An analysis of the time devoted to the practice of PA and ST every day was made for each child. Discussions were held with the children about these data and strategies to further increase PA and decrease ST. They identified and worked on barriers to PA practice.
Workshop 7: “Have I changed my PA practice? Am I trying to be less sedentary?” and “What did I learn about PA and ST?”	An assessment was made with children on behavioral changes in terms of PA and ST and on the knowledge acquired on PA, ST, and more generally on health.
Workshop 8: Drawing contest	A drawing contest on the theme “I’m moving” was done at the end of the intervention period.
Activities in the schoolyard: “What games can I play...?”	A session was organized in the schoolyard to identify games that can be played in the schoolyard or in leisure time, alone or with friends. For example: “what games can I play with a cord?” The children imagined and listed games and demonstrated them.
Active classroom: “Spelling and mathematics”	Demonstration of active classroom workshops for further use by the teachers: “Spelling activity,” in which children had to touch different parts of the body while spelling out the letters of words. The words were more or less complicated depending on the grade of the children. (2) “Arithmetic exercise,” in which children had to make a jump after having said the result of the addition or multiplication.
Sedentary breaks: “Relaxation and breathing”	The activity break included breathing, relaxation, and visualization exercises, or body movements such as motor coordination, balance, and flexibility exercises. These sedentary breaks did not include academic knowledge.
Activities outside of school: Photovoice workshop	Excursion to the school neighborhood to observe the areas in which one can practice PA and to identify the areas dangerous for practice. The children took pictures of the different areas with tablets. Back in class, the children showed their photos to their classmates and explained why they took this picture (if it was possible to practice PA in this area, or if it was a dangerous area).
Feedback	Individual summary sheets with PA and ST levels and performance at the different motor tests were given to each child in a graphic format after each assessment. Explanations and consideration took place in the classroom.
Interpersonal (level 2): parents	
Information meeting	The overall project was presented (ie, all the activities planned for parents and children and teachers, school, and the involvement of local political groups).
Workshop 1: “What is PA?” and “How to practice PA?”	Information about PA was given. Consideration of the different opportunities to practice PA: for the parents themselves and with their children. Facilitators and barriers to PA practice were identified.

Theme of each action according to the level of the socioecological level	Content
Workshop 2: "What is ST?"	Information about ST was given: different sedentary behaviors they can have in a day and the effect of cumulative ST on health. This included the study of different possibilities to decrease ST at each time of the day for them and their child.
Workshop 3: "How can I influence my child's PA? How do my child's friends influence him/her in his/her practice of PA and health behaviors?"	The influence of parents and friends on the health behaviors of the child was studied.
Workshop 4: "Is the environment adapted to practice physical activity?"	The different pictures taken by the children in the "Photovoice Workshop" were analyzed and discussed. A special point was made about the facilitators and the barriers to practice of PA, for them and for their children.
Workshop 5: "Have I changed my PA practice? Am I trying to be less sedentary? Is this also the case for my child? What did I learn about PA and ST?"	An assessment was made of their own behavioral changes in terms of PA and ST as well as for their child and of the knowledge acquired with these workshops on PA, ST, and more generally on health.
Newsletter	After each workshop, all parents received a newsletter with the principal information given during the workshop.
Feedback	Individual summary sheets with PA and ST levels and performance at the different motor tests were given to each child in a graphic format after each assessment. Parents had access to these.
Interpersonal (level 2): teachers	
Workshop 1: "What is PA? What is ST and sedentary habits?"	Theoretical knowledge about PA and ST was proposed.
Workshop 2: Strategic issues to increase children's PA	Consideration of how to include information related to PA in classes: how to increase PA and decrease ST at school and especially in the classroom.
Workshop 3: Concrete formation on active classroom and sedentary break activities	Ideas on how to conduct an active classroom were presented: (1) proposal of active classroom exercises and sedentary breaks (breathing, relaxation, and visualization exercises, or body movements such as motor coordination, balance, and flexibility exercises); (2) advice and guidance on the implementation; (3) material organization of the classroom to increase movement, etc.
Workshop 4: Main influences around the children	A discussion was held on the influence of parents, friends, and teachers on children's health behaviors. Then the environmental factors facilitating, or not, the practice PA were discussed. This led to the construction of a multilevel model and the presentation of the principal theories used in this study (ie, the socioecological model and the self-determination theory).
Workshop 5: Final assessment of the program intervention	An assessment of the school-based actions they had implemented was made: a discussion on their opinion about the intervention, its strength and weaknesses, and its effects on their PA and ST behaviors as well as on the children's and their parents.
Feedback	The general PA and ST levels were presented to the teachers after each assessment.
Environmental (level 3): school	
Physical and material modifications of the schoolyard	After children's workshop 4, each class made a design proposal for the schoolyard (marks to be drawn and materials to add for recess). An assessment of these proposals was made with the teachers, the research team, and the representatives of the education department of the town hall, and a choice was made about the implementation of the material required. It led to delineation of different games in the different schoolyards (ie, football field, squares with numbers and letters, snail hopscotch) and acquisition of small material (ie, balls, ropes).

Theme of each action according to the level of the socioecological level	Content
Organizational modifications of lunch break	In line with the baseline measurement analyses, actions to reduce ST during lunch break were engaged in cooperation with the canteen's agents and services. The aim was to move from 90 minutes of sitting time to 50-60 minutes in order to free up time to play in the schoolyard before going back to the classroom. Thus, the research team proposed changes to the organization (ie, 2 canteen services, table-based group organization) from which the educators in charge of lunch time made a choice.
Organizational modifications of recess games	The schoolyard was divided into different areas dedicated to specific games during recess and lunch time. This provided an opportunity to have a diversity of games and sports to play together or alone (instead of having one game/sport taking all the schoolyard). The schedule was proposed by the children and supervised by the teachers.
Political (level 4): local politic groups	
Collaboration with the city town hall	The city town hall helped in the implementation of the intervention. It allowed the interactions with the canteen agents for the reorganization of the lunch time and the drawings in the schoolyard were made by the education service of the city.
Collaboration with national education authorities	They authorized the implementation of the school-based intervention and helped with the organization of the actions. In addition, these authorities made it possible to officially validate the training for teachers as part of their professional learning curriculum.
Study developed by "CAPAS-City"	This study was conducted by CAPAS-City (founded by the European Regional Development Fund [FEDER]): this center is in charge of developing PA programs and promotions actions.

Ethics Approval and Consent to Participate

This study has been approved by the Comité de Protection des Personnes Sud Mediterranée III and has been registered at ClinicalTrials.gov under the identifier NCT03983447. Parents/guardians were informed of the intervention project by a written letter. This letter contained a consent form. Afterward, a public meeting with the research team was organized in each school so that parents could come to ask any questions. Then, one of the parents or guardians had to sign the consent form in order to permit the children's participation in the study. The parents/guardians had to give this consent form to the child, who gave it to the teachers. The researchers collected the consent forms either directly after the meeting or later from the teachers.

Availability of Data and Materials

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Results

The presented intervention and the different assessments have been successfully implemented. In order to achieve the 2 objectives of this randomized controlled trial, data analyses are about to be completed. Two articles are planned: the first one will evaluate the effectiveness of the multicomponent school-based intervention and the second one will study the relationships between PA, ST, motors skills, attentional capacities, and academic achievement.

Discussion

The most recent literature review found a lack of evidence for the effectiveness of school-based and multileveled interventions to promote PA, despite the fact that those using the socioecological model are among the most promising [10,11,17].

Thus, this article presents an improved experimental methodology in order to (1) evaluate the effectiveness of a school-based intervention to promote PA and reduce ST and (2) examine the relationships between PA, motor skills, attentional capacity, and academic achievement among disadvantaged primary school children. It can thus contribute to providing crucial information in the field of PA promotion during childhood. First, our experimental methodology used accelerometry, which is an objective method to measure PA and ST. Second, the longitudinal aspect of our study provides a follow-up for a diversity of variables related to movement and cognition over successive years during childhood. These longitudinal measures lead to a more precise understanding of the evolution of the interventional effects from the diagnostic to the follow-up measurements. Finally, the configuration of our study makes it possible to measure potentially indirect effects of the intervention on motor skills and attentional capacities.

An important aspect of this study is that the actions implemented in this intervention are not only based on the relevant literature [10-24], but also on the principal outcomes from the baseline measurement concerning PA and ST. As a consequence, the intervention has been adapted to the context and to the specific needs, which probably contributes to its effectiveness together with the fact that it has been constructed with the different actors

involved and that it addresses the different levels of the socioecological model [19]. The description of this protocol could be of use to researchers in the field of PA promotion as well as to teachers of children from disadvantaged neighborhoods, to help them design actions facilitating well-being and academic success in the relevant social climate. In the long term, the objective of this project is to carry out the school-based intervention to promote PA and decrease ST in several primary schools of this French city. The next step will be to replicate the same intervention in the school that has been assigned as a control group. The effectiveness of this next intervention will also be studied.

In conclusion, physical inactivity and sedentary behavior are major public health problems. The implementation of this randomized controlled trial can help to determine effective strategies to promote PA in the context of increasing prevalence of physical inactivity among children with sedentary lifestyles. Understanding these strategies is a real necessity for researchers, stakeholders, and public policy makers seeking to establish health promotional actions for the population.

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Authors' Contributions

CB conducted the study, coordinated, supervised the data collection, drafted the initial manuscript and approved the final manuscript submitted. LL and JB critically reviewed the manuscript and approved the final manuscript submitted. NF helped design the study, coordinated the data collection.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-EHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 444 KB - resprot_v9i9e17815_app1.pdf]

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Abbreviations

FAS II: Family Affluence Scale II
MVPA: moderate to vigorous physical activity
PA: physical activity
ST: sedentary time
WHO: World Health Organization

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Protocol

Telomerase Activation to Reverse Immunosenescence in Elderly Patients With Acute Coronary Syndrome: Protocol for a Randomized Pilot Trial

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Abstract

Background: Inflammation plays a key role in the pathophysiology of coronary heart disease (CHD) and its acute manifestation, acute coronary syndrome (ACS). Aging is associated with a decline of the immune system, a process known as immunosenescence. This is characterized by an increase in highly proinflammatory T cells that are involved in CHD progression, plaque destabilization, and myocardial ischemia–reperfusion injury. Telomere dysfunction has been implicated in immunosenescence of T lymphocytes. Telomerase is the enzyme responsible for maintaining telomeres during cell divisions. It has a protective effect on cells under oxidative stress and helps regulate flow-mediated dilation in microvasculature.

Objective: The TACTIC (Telomerase ACTivator to reverse Immunosenescence in Acute Coronary Syndrome) trial will investigate whether a telomerase activator, TA-65MD, can reduce the proportion of senescent T cells in patients with ACS with confirmed CHD. It will also assess the effect of TA-65MD on decreasing telomere shortening, reducing oxidative stress, and improving endothelial function.

Methods: The study was designed as a single-center, randomized, double-blind, parallel-group, placebo-controlled phase II trial. Recruitment started in January 2019. A total of 90 patients, aged 65 years or older, with treated ACS who have had CHD confirmed by angiography will be enrolled. They will be randomized to one of two groups: TA-65MD oral therapy (8 mg twice daily) or placebo taken for 12 months. The primary outcome is the effect on immunosenescence determined by a decrease in the proportion of CD8+ TEMRA (T effector memory cells re-expressing CD45RA [CD45 expressing exon A]) cells at 12 months. Secondary outcomes include leukocyte telomere length, endothelial function, cardiac function as measured by echocardiography and NT-proBNP (N-terminal fragment of the prohormone brain-type natriuretic peptide), systemic inflammation, oxidative stress, and telomerase activity.

Results: The study received National Health Service (NHS) ethics approval on August 9, 2018; Medicines and Healthcare products Regulatory Agency approval on October 19, 2018; and NHS Health Research Authority approval on October 22, 2018. The trial began recruiting participants in January 2019 and completed recruitment in March 2020; the trial is due to report results in 2021.

Conclusions: This pilot trial in older patients with CHD will explore outcomes not previously investigated outside in vitro or preclinical models. The robust design ensures that bias has been minimized. Should the results indicate reduced frequency of

immunosenescent CD8+ T cells as well as improvements in telomere length and endothelial function, we will plan a larger, multicenter trial in patients to determine if TA-65MD is beneficial in the treatment of CHD in elderly patients.

Trial Registration: ISRCTN Registry ISRCTN16613292; http://www.isrctn.com/ISRCTN16613292 and European Union Drug Regulating Authorities Clinical Trials Database (EudraCT), European Union Clinical Trials Register 2017-002876-26; https://tinyurl.com/y4m2so8g

International Registered Report Identifier (IRRID): DERR1-10.2196/19456

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KEYWORDS

coronary heart disease; acute coronary syndrome; immunosenescence; telomerase activator

Introduction

Background

Inflammation plays a key part in the pathophysiology of coronary heart disease (CHD) and its acute manifestation—acute coronary syndrome (ACS)—from atheroma formation to plaque rupture [1]. Despite contemporary treatment, recurrent adverse events (AEs) post-ACS remain common, especially in the elderly [2]. Aging is associated with a decline of the immune system, a process known as immunosenescence [3], leading to an increased burden of disease. Targeting interleukin 1 (IL-1β), the principal cytokine of innate immunity, in patients with previous myocardial infarction (MI) has been shown to reduce subsequent adverse cardiovascular outcomes [4]. Furthermore, the contribution of the adaptive immune system to the complex inflammatory response evoked during ACS has been demonstrated extensively in experimental and clinical studies [5]. In particular, highly proinflammatory senescent T cells are thought to be key players in plaque destabilization [6] and myocardial ischemia–reperfusion injury [7].

Telomere dysfunction has been implicated in immunosenescence of T cells [3,8]. Telomeres are DNA caps that protect the ends of chromosomal DNA. They are widely regarded as the internal biological clock of a living organism and shorten by a few base pairs with every cell division. This process can be slowed down by activation of telomerase, which is responsible for producing and maintaining telomeres. Shorter lymphocyte telomeres are associated with development of CHD as well as increased cardiovascular risk and mortality independent of conventional vascular risk factors [9-12]. Alleles associated with shorter telomere length (TL) were also associated with an increased risk of CHD, suggesting a causal relationship [13].

The TACTIC (Telomerase ACTivator to reverse Immunosenescence in Acute Coronary Syndrome) trial was designed to test whether a telomerase activator can reduce the proportion of senescent T cells in patients following ACS. There is accumulating evidence that telomerase, through its telomerase reverse transcriptase (TERT) catalytic subunit, contributes to cell physiology independently of its ability to elongate telomeres. We and our collaborators have demonstrated the effect of oxidative stress on telomerase as well as a telomere-independent protective effect of telomerase in cells under oxidative stress [14,15]. Telomerase activity (TA) has also been shown to regulate endothelial flow-mediated dilation (FMD) [16].

The small molecule cycloastragenol (CAG), isolated from the roots of the herb astragalus, is the only available telomerase activator in humans. TA-65MD is a purified and encapsulated form of CAG with increased bioavailability (T.A. Sciences). We have also shown that TA-65MD induces telomerase and proliferation in CD4 T lymphocytes in a TERT-dependent way [17]. In a randomized controlled trial investigating cytomegalovirus (CMV)-positive healthy subjects aged 53-87 years old, subjects taking 8 mg of TA-65MD daily increased TL over the 12-month period, whereas subjects in the placebo group significantly lost TL [18].

Trial Rationale

The evidence indicates that telomerase deficiency in atherosclerosis leads to accelerated immunosenescence with telomere shortening in peripheral blood leukocytes, increased oxidative stress and inflammation, and impaired microvascular endothelial function, all of which contribute to CHD progression. We hypothesize that activating telomerase with TA-65MD will lead to reduced immunosenescence, decreased telomere shortening, and improved endothelial function in patients with CHD. The null hypothesis is that there will be no difference in immunosenescence between the two groups following 12 months of treatment with TA-65MD or placebo. The choice of active treatment versus placebo is appropriate in this population where no telomerase activator is currently used as part of usual care. All patients will receive usual care alongside the trial.

Objectives

Primary Objective

We aim to assess the effect of 8 mg of oral TA-65MD given twice daily for 12 months on immunosenescence in older patients following ACS.

Secondary Objectives

The secondary objectives of this trial are as follows:

1. To investigate the effect of 1-year TA-65MD treatment on leukocyte TL.
2. To investigate the effect of 1-year TA-65MD treatment on microvascular endothelial function.
3. To investigate the effect of 1-year TA-65MD treatment on systemic inflammation and heart failure, reflected by expression of N-terminal fragment of the prohormone brain-type natriuretic peptide (NT-proBNP) and high‐sensitivity C‐reactive protein (hsCRP).

4. To investigate the effect of 1-year TA-65MD treatment on measures of cardiac function as measured by echocardiography.
5. To investigate the effect of TA-65MD treatment on TA and oxidative stress.
6. To investigate the effect of TA-65MD treatment on clinical events—all-cause death, stroke, or MI—in patients after 1 year.
7. To characterize the AE profile of TA-65MD.
8. To quantify adherence to study drugs.
9. To investigate the impact of seropositivity to CMV at baseline on trial outcomes.

Methods

Trial Design

This is a single-center, randomized, double-blind, parallel-group, placebo-controlled phase II trial comparing TA-65MD with placebo in 90 participants with CHD who have had ACS in the 6 months prior to consent. A total of 90 patients will be randomized to either the TA-65MD group (n=45) or the placebo group (n=45); TA-65MD and placebo will be taken by these groups, respectively, twice daily for 12 months. The schedule of this trial is shown in Table 1. The trial will run according the International Conference on Harmonisation (ICH)-Good Clinical Practice (GCP) and in accordance with relevant UK legislation and the trial protocol. This trial was registered at the International Standard Randomized Controlled Trial Number (ISRCTN) registry (16613292) and at the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT), European Union Clinical Trials Register (2017-002876-26).

Table 1. Trial schedule of assessments and interventions.

Schedule items	Time of assessments and interventions						
	Baseline[a]	Day 1	1 month (wks 3-5)	3 months (wks 11-15)	6 months (wks 24-28)	9 months (wks 37-41)	12 months (wks 50-54)
Enrollment							
Eligibility screen	X						
Informed consent	X						
Assessments							
Blood pressure	X		X	X	X	X	X
Capillary glucose	X		X	X	X	X	X
Physical assessment of height and weight	X						
Venous sample (5 mL) cytomegalovirus IgG[b]	X						
Venous sample (4 mL) CD8 TEMRA[c] immunosenescence (primary outcome)[d]	X				X		X
Venous sample (36 mL) CD8 and CD4 immunosenescence (secondary outcomes), telomere length, and telomerase activity	X				X		X
Venous sample (4 mL) oxidative stress, future use	X				X		X
Venous sample (5 mL) future research use—optional consent	X				X		X
Venous sample (5mL) hsCRP[e] and NT-proBNP[f]	X				X		X
Endothelial function (EndoPAT [Peripheral Arterial Tone])	X				X		X
Echocardiography	X						X
Interventions							
Randomization—stratified	X						
Dispensing of investigational medicinal product (IMP)		X	X	X	X	X	X
Return of unused IMP and drug adherence			X	X	X	X	X
Adverse events evaluation			X	X	X	X	X

[a]Baseline assessments are completed after written consent is obtained and are performed before randomization.

[b]IgG: immunoglobulin G.

[c]TEMRA: T effector memory cells re-expressing CD45RA (CD45 expressing exon A).

[d]Results from baseline immunosenescence sample are required for randomization.

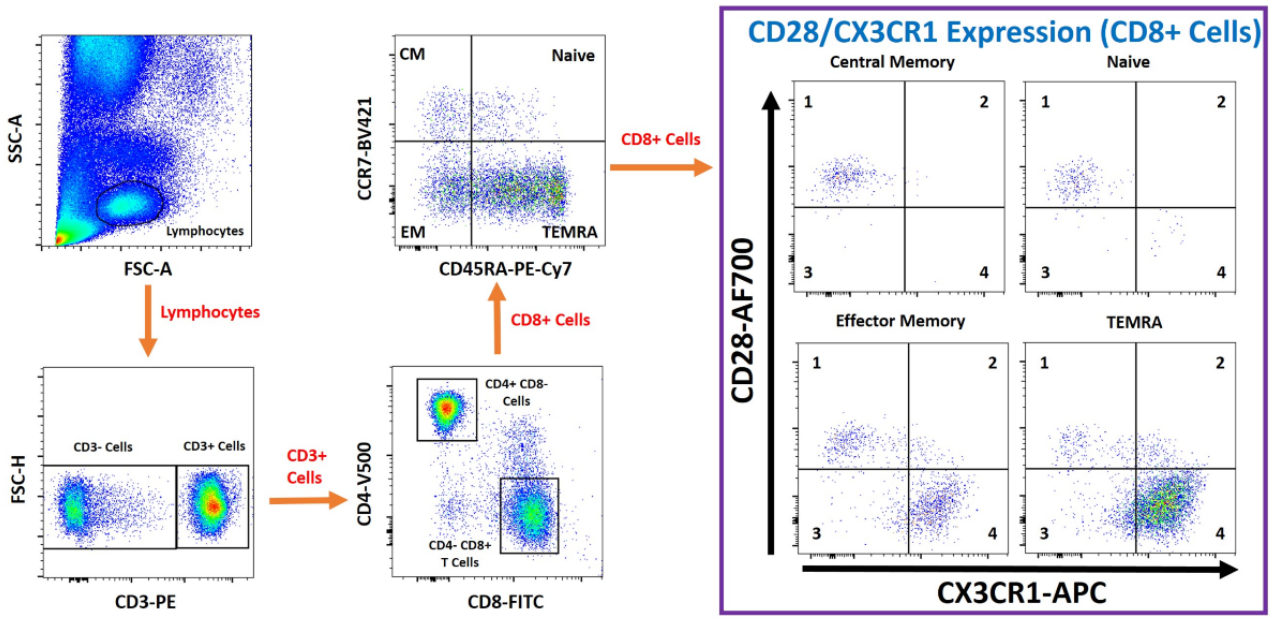
[e]hsCRP: high - sensitivity C - reactive protein.

[f]NT-proBNP: N-terminal fragment of the prohormone brain-type natriuretic peptide.

Primary Outcome

The primary outcome is immunosenescence following 12 months of treatment with TA-65MD. Immunosenescence will be determined by flow cytometry and fluorescence-activated cell sorting (FACS) (see Figure 1); the proportion of terminally differentiated CD8+ effector memory cells (% CD8+ TEMRA [T effector memory cells re-expressing CD45RA (CD45 expressing exon A)]) will be calculated from the total number of peripheral blood CD8+ T lymphocytes. We have previously demonstrated the prognostic utility of CD8+ TEMRA as a measure for immunosenescence [19]. The mean difference between the intervention and control arms will be compared at 12 months.

Figure 1. Example gating path for seven-color fluorescence-activated cell sorting (FACS) from ethylenediaminetetraacetic acid (EDTA) peripheral blood. AF700: Alexa Fluor 700; APC: allophycocyanin; BV421: Brillian Violet 421; CCR7: C-C chemokine receptor type 7; CD45RA: CD45 expressing exon A; CM: central memory; CX3CR1: C-X3-C motif chemokine receptor 1; EM: effector memory; FITC: fluorescein isothiocyanate; FSC: forward scatter; FSC-H: forward scatter-pulse height; PE: phycoerythrin; PE-Cy7: phycoerythrin and cyanine 7; SSC: side scatter; TEMRA: T effector memory cells re-expressing CD45RA; V500: violet 500.



Secondary Outcomes

CD8 T Cell Telomere Length

TL will be determined from cryopreserved peripheral blood mononuclear cells (PBMCs) by flow cytometry-fluorescent in situ hybridization (flow-FISH) [9]. TL will be measured in total leukocytes and CD8+ T cells. CD8+ T cell TL is significantly reduced in patients with CHD and post-MI [9]. We expect TL in CD8+ T cells to decrease less in patients treated with TA-65MD. TL will be measured in total leukocytes and in CD8+ T cells at baseline, 6 months, and 12 months.

Microvascular Endothelial Function

Microvascular endothelial function will be assessed by measuring FMD at baseline, 6 months, and 12 months. Using plethysmography at the fingertips of both hands, the EndoPAT (Peripheral Arterial Tone) system (Itamar Medical Ltd) will calculate an index of pulse wave amplitude after cuff occlusion to before occlusion of the test arm divided by the same ratio of the control arm, namely the reactive hyperemic index. FMD has been shown to be compromised in patients with CHD and microvascular dysfunction as a predictor of adverse clinical outcome [20].

Systemic Inflammation

Systemic inflammation will be assessed using the hsCRP, which is a downstream biomarker of inflammation associated with an increased risk of cardiovascular events [21].

Cardiac Function

Cardiac function will be assessed by NT-proBNP and transthoracic echocardiography at baseline and 12 months. Together, these measures will determine myocardial function, strain (NT-proBNP), and global longitudinal strain, reflecting the pathophysiological targets of heart failure. Lack of telomerase and presence of shortened telomeres in cardiomyocytes from preclinical models (ie, mice) have been shown to be critical in the development of heart failure in that species [22]. Patients with chronic heart failure have shorter TL compared to age- and gender-matched controls with incremental attrition according to the presence and extent of coronary artery disease (CAD) [23].

Telomerase Activity

TA will be assessed by a modified telomeric repeat amplification protocol (TRAP) assay, using digital droplet polymerase chain reaction (PCR) [24,25]. This provides an indication of drug effect: TA-65MD is expected to increase TA in PBMCs.

Oxidative Stress

Oxidative stress will be measured with the thiobarbituric acid reactive substances (TBARS) colorimetric assay (Oxford Biomedical Research) from freshly collected and cryopreserved plasma. TBARS is an established assay to quantify lipid peroxides [26].

Seropositivity to Cytomegalovirus

The effect of CMV seropositivity at baseline will be correlated with study outcomes using an exploratory analysis. CMV is a highly prevalent human herpes virus with CMV seropositivity present in a large proportion of elderly patients. CMV-directed cells increase with age, constituting a large proportion of the total CD8+ T cell pool in elderly individuals [27]. T cell responses to CMV are restricted to a limited number of epitopes, resulting in progressive, prolonged oligoclonal expansion of CMV-specific CD8+ T cells in a process known as memory inflation [28]. We have previously shown that individuals who are seropositive have a much higher proportion of CD8+ TEMRA cells and have a greater risk of heart attacks [7,29].

Clinical Outcomes and Adverse Events

Major clinical events will be measured for 12 months from the start of treatment. All-cause death, MI, and stroke will be presented as a composite outcome—major adverse cardiac and cerebrovascular events (MACCE)—and also reported separately. All AEs, including those considered related and unrelated to the intervention, will be recorded and reported from the time of randomization for 12 months or until a patient has completed all trial activities.

Study Setting

The trial aims to recruit 90 patients. All patients will be recruited, treated, and followed up at a single site: The James Cook University Hospital, Middlesbrough, UK. Blood samples will be analyzed at site laboratories and, where specialist equipment and expertise are required, will be transported to the Institute of Genetic Medicine, Newcastle University, UK, for analysis.

Study Visits and Assessments

Following baseline assessment and initiation of treatment—placebo or TA-65MD—patients in both groups will be followed up at 1 month, 3 months, 6 months, 9 months, and 12 months (see Table 1). At each visit, drug adherence will be assessed and the patient will be evaluated for AEs.

Inclusion and Exclusion Criteria

Textbox 1 lists the criteria informing the eligibility or exclusion of patients for the trial.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria—patients will be eligible for the trial if they:

- Provide written informed consent
- Are male or female, aged 65 years or over, with an index presentation of an acute coronary syndrome (ACS)* within the previous 6 months
- Have successfully completed revascularization** or are being managed medically following ACS
- Have angiographic evidence of coronary heart disease: at least one major epicardial vessel stenosis ≥70%
- Are recruited more than 24 hours after presentation with the index ACS event

*ACS defined as either a non-ST elevation myocardial infarction (NSTEMI) or ST elevation myocardial infarction (STEMI)

**Percutaneous coronary intervention or angioplasty, eligible the following day, or coronary artery bypass grafting, eligible 3 months following surgery

Exclusion criteria—patients will be excluded from the trial if they:

- Have any disorder associated with immunological dysfunction (ie, acute or chronic inflammatory or neoplastic coexisting disease, known positive serology for HIV, or hepatitis)
- Are clinically unstable (ie, hemodynamically unstable, cardiogenic shock, or unconscious)
- Have severe, uncontrolled hypertension (blood pressure [BP] >170/110 mmHg or ambulatory BP of 150/95 mmHg)
- Have a severe comorbidity that has impact on outcome over the next 2 years
- Are taking immunosuppressants
- Have a known malignancy
- Currently use a nutritional supplement derived from the roots of the

  Astragalus

  species
- Have a previous known substance addiction
- Have insulin-dependent diabetes
- Are judged by the investigator that they should not participate in the study, for example, on the basis of previous serious psychiatric illness or are unlikely to comply with study procedures, restrictions, and requirements
- Have participated in any other interventional medicinal study in the past 6 months

Trial Procedures

Screening, Recruitment, and Consent of Participants

Potential participants will be identified by the clinical team following admission to hospital with ACS and having agreed to undergo coronary angiography or having already had an angiography that confirms CHD. Patients may also be identified following discharge. Potentially eligible participants will be invited to participate by a delegated member of the study team. The trial will be explained by the clinical research team and, after time for questions, written consent will be sought from the patient. Written informed consent will be obtained prior to any trial specific procedures and prior to randomization. There will be additional consent for storage of blood samples for up to 5 years for future use in ancillary studies. Patients have the right to withdraw from the trial at any time and without

providing a reason. With the explicit consent of patients, general practitioners will be informed of their participation.

Eligibility Assessment

Following consent, the principal investigator or a subinvestigator on the delegation log will confirm the patient's eligibility. Patients who do not meet trial eligibility criteria prior to randomization will be considered a *screen failure* and withdrawn from the trial with no further data collected.

Randomization

Randomization will be performed using the Sealed Envelope Ltd system with a minimization scheme to ensure patients randomized to each group are comparable at baseline. The minimization scheme will account for (1) gender (male or female), (2) type of ACS (ST elevation myocardial infarction [STEMI] or non-ST elevation myocardial infarction [NSTEMI]), and (3) CD8+ TEMRA (high >45% or low ≤45%) at baseline.

Eligible patients will be randomized by delegated and trained members of the research team at each center using the 24-hour, central, secure, web-based randomization system with concealed allocation. Eligible patients will be randomized in a 1:1 ratio to receive TA-65MD (intervention under study) or placebo (control arm).

Blinding

Assignment to either the TA-65MD or placebo groups will be blinded to the patient, treating clinicians, and the clinical research team, including the pharmacy, research nurses, echocardiogram assessors, laboratory staff, and the chief investigator. Blinding will be maintained in the randomization system, the electronic case report forms (eCRFs), and on investigational medicinal product (IMP) labels. All members of the Newcastle Clinical Trial Unit (NCTU) and the statistics team will be blinded, with the exception of the trial data manager to enable reporting to the independent data monitoring committee as appropriate. The IMP will be labeled using a unique identification code, which will be linked to the study randomization system. TA-65MD and its matched placebo will be identical and presented in the same packaging to ensure blinding of the IMP.

Unblinding

Unblinding should not occur except in the case of medical emergencies, where the appropriate management of the patient requires the knowledge of the randomization allocation. To avoid unnecessary unblinding, it will be assumed that the patient is on active treatment within the trial. The Sealed Envelope Ltd online web-based randomization service will be used for emergency unblinding. The primary trial analysis will be performed prior to unblinding. All patients will be informed of which arm they were assigned to, once analysis of the trial data is complete.

Study Intervention

Intervention Under Study: TA-65MD

TA-65MD is marketed as a dietary supplement. The active ingredient of TA-65MD is 1.8% CAG, isolated from roots of the *Astragalus* species. The active ingredient has been identified in an empirical screen of traditional Chinese medicine plant extracts and compounds. TA-65MD is an activator of telomerase, an enzyme whose actions protect the ends of chromosomes from shortening associated with repeated cellular replication. Patients allocated to the intervention will be given 8 mg of TA-65MD twice daily.

Control Arm: Placebo

The matched placebo has been manufactured to ensure that it is consistent with TA-65MD in appearance, taste and smell, labeling, packaging, and batch number. Patients allocated to the placebo group will be given this twice daily.

Safety Data

Overview

An independent expert panel has determined TA-65MD to be Generally Recognized As Safe (GRAS) for use in a medical food under the provisions of the Federal Food, Drug, and Cosmetic Act, administered by the US Food and Drug Administration. T.A. Sciences, Inc, provided extensive animal and human clinical data to support the status of GRAS. The safety of TA-65MD has been assessed in an observational study of 114 adults over the course of 1 year [30]. At doses up to 50 mg per day there were no AEs reported for TA-65MD. Safety was also assessed in a randomized, placebo-controlled study involving 117 adult volunteers over the course of 1 year, with no toxicities detected in the liver, kidneys, and metabolic functions as assessed by biochemical markers [29]. An anticipated risk for the use of TA-65MD relates to its ability to activate telomerase. This is the subject of scientific conjecture in consideration of its relationship to cancer [31,32]. An in vitro assay testing the telomerase-activating potency of TA-65 (ie, CAG not in capsules) in Medical Research Council cell strain-5 (MRC-5) fibroblasts suggested there was dose-related TA (Sierra Sciences Labs). While telomerase activation has been observed, TA-65MD does not increase the lifespan of cells. In fact, the preliminary observation of a controlled in vivo cancer study using 5 mL/kg of TA-65 (ie, CAG not in capsules) or sham drug administered by oral gavage for up to 40 days in mice xenografted with four different human tumors—lung (H460), colon (HT29), breast (MDA-MB-435), and prostate (PC3)—suggests a trend toward tumor growth retardation in two cancer types; as well, there was no statistically significant adverse effects on body weight or tumor size for any of the cell lines nor on the growth rate of the tumors (internal T.A. Sciences document, 2008). Given that the population under study in the TACTIC trial are elderly with ACS, and that there were no data on the impact of the drug on the outcomes or population, we chose to conduct the trial using a conservative dose of 8 mg twice daily.

Known Side Effects

TA-65MD may interfere with medications that suppress the immune system and may also affect blood sugar and blood pressure. In an observational study, two subjects self-reported an "anxious" feeling shortly after voluntarily increasing their daily consumption of TA-65MD to 100 mg/day—a self-imposed choice without physician approval at a consumption level two times above the intended dose for this observational study; the

feelings resolved in both subjects when daily consumption was returned to 50 mg/day.

Administration and Adherence

Participants may begin taking the IMP immediately following the completion of all baseline assessments, confirmation of eligibility, and randomization. A dose of 8 mg of TA-65MD (T.A. Sciences) or matched placebo will be taken as 1 × 8-mg capsule twice daily (ie, morning and evening). Participants will take the allocated IMP until the end of follow-up at 12 months. Patients will be prescribed IMP following randomization and at 1, 3, 6, and 9 months following the start of the intervention. Returned capsules at each visit will be used to calculate the adherence for each participant. Concomitant medications will also be reviewed and documented at each visit.

Withdrawal of Participants

Participants will be made aware of their right to withdraw from the trial at any time for any reason and without giving a reason. Participants will be withdrawn from the trial by the clinical team for any of the following reasons:

1. Intercurrent illness means the participant is no longer able to complete study procedures.
2. The patient suffers unacceptable side effects caused by the study drug.
3. Suspected unexpected serious adverse reactions occur.

The investigator can withdraw participants in the event of any reason that would compromise participant safety or the validity of the results. Data and blood samples collected up to the point of withdrawal will be kept and used in the analysis of the trial unless the participant explicitly requests for these to be removed.

Pharmacovigilance

All AEs will be recorded in the participants' medical notes and on the eCRFs. AEs will be recorded from the day of randomization until the last visit or until withdrawal, with the exception of those considered related to the IMP, which will be followed until resolution, a stable outcome, or death. All AEs are assessed for severity, causality, expectedness, and seriousness by an investigator; all are reviewed by the Independent Data Monitoring and Ethics Committee (IDMEC). In accordance with current legislation, AEs will, where necessary, undergo expedited reporting to the sponsor and to the Medicines and Healthcare products Regulatory Agency (MHRA) within the required timelines.

Statistical Considerations

Overview

A pragmatic decision was taken to recruit and analyze data on 90 patients: 45 in each group. This sample size is the minimum conventional threshold for making parameter estimates in pilot studies [33]. The parameter estimates in this trial will be used to inform a large, multicenter clinical trial.

Data Management

Study data are recorded in each patient's medical notes before being recorded onto eCRFs, which are developed and managed by the NCTU. The eCRF has been built using the Red Pill system supplied by Sealed Envelope Ltd. Data entered onto the eCRF must be consistent with the information in the medical notes. Patients are identified using a unique study ID; all data passed to the NCTU will have patient identifiers removed, with the exception of date of birth, gender, ethnicity, and study ID. Data cleaning is provided by staff within the NCTU.

Statistical Analysis

Primary analysis will follow intention-to-treat principles with patient data analyzed according to randomization and irrespective of intervention received; other analysis groups, such as per-protocol groups, may be considered subsequently. Every effort will be made to retain and include all patients who are part of the trial.

Data will be summarized by study group. Mean or median will summarize continuous variables, whereas number and percentage will be used to summarize categorical variables. A general linear model will be used to analyze the primary outcome considering all covariates used in the randomization scheme. Similar methods will be used to analyze all continuous secondary outcomes. Data of other types will be analyzed using generalized linear models with appropriate distributions.

The numbers of MACCE after 12 months will be compared between arms by the use of standardized rates (eg, by consideration of the number of events per patient month in each arm). Impact of missing data will be explored by tabulating the proportion of missing data in each arm. A full statistical analysis plan will be developed for the outcome measures and agreed upon with the IDMEC and the chief investigator prior to any analysis being undertaken.

Trial Governance

The trial is sponsored by South Tees Hospitals National Health Service (NHS) Foundation Trust and funded by T.A. Sciences, Inc, New York, USA. The trial is being run in collaboration with the NCTU at Newcastle University. The sponsor and funder were not involved in the trial design. The sponsor has delegated the trial design; collection, management, analysis, and interpretation of data; report writing; and publications to the chief investigator and coinvestigators. The trial is overseen by the Trial Steering Committee, which meets every 6 months and includes an independent chair and two other independent members, one of whom is a patient. In addition, the trial includes the IDMEC, which meets every 6 months and oversees all ethical and safety issues in accordance with a study-specific DAMOCLES (Data Monitoring Committees: Lessons, Ethics, and Statistics) charter. All members are independent of the study team, although the trial manager, chief investigator, and some other members of the Trial Management Group attend the open sessions in order to inform the committee about the trial progress. The IDMEC makes recommendations to the Trial Steering Committee. The day-to-day supervision of the trial will be the responsibility of the Trial Management Group, who report to the Trial Steering Committee.

Dissemination and Publications Policy

The trial will be published in peer-reviewed journals following the end of the trial, and the data will be presented at national

and international meetings. We do not intend to use professional writers. Results of the trial will also be reported to the funder, sponsor, and the Research Ethics Committee within one year after the end of the trial. Trial participants will be informed about the trial results and their treatment allocation at the end of the trial, including a lay summary. The datasets analyzed during this study are available from the corresponding author on reasonable request.

Results

The study received NHS ethics approval on August 9, 2018; MHRA approval on October 19, 2018; and NHS Health Research Authority approval on October 22, 2018. The trial began recruiting participants in January 2019 and completed recruitment in March 2020; the trial is due to report results in 2021.

During the COVID-19 pandemic, all patients will have their visits carried out remotely. Primary and secondary outcome measures that are not able to be carried out remotely will occur later than planned, on-site, as soon as it is safe for the patients to do so and when laboratories are able to process and analyze trial samples. Measures of blood pressure and blood glucose will be undertaken by patients who have not yet attended the site for their 6-month visit. Portable blood pressure monitors and blood glucose monitors will be sent to those patients to be used to record their results at home when required as per the schedule of events for the duration of the pandemic. Some patients may require continuation of the IMP beyond 12 months to enable them to attend the hospital for their final trial visit assessments. The 6-month and 12-month visits will occur as soon as it is safe for this group of patients to attend the hospital and when the trial laboratories are able to accommodate processing and analysis of trial samples.

Discussion

ACS, the acute manifestation of atherosclerosis, is a leading cause of mortality and morbidity. Age is an independent risk factor for adverse cardiovascular outcomes after ACS, and this is likely related to upregulation of the inflammatory response that occurs with aging. Improvements in cardiovascular outcomes over the last two decades have been realized mainly in younger patients [34]. There remains an unmet need for novel therapeutic approaches in older patients following ACS [35,36].

The CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study) trial has provided strong evidence for the critical role of inflammation in atherosclerosis by showing that canakinumab—a human monoclonal anti-IL-1β antibody—led to a reduction in major cardiovascular events independent of lipid-level lowering [4]. Canakinumab was associated with a higher incidence of nonfatal infection, potentially limiting its use in older patients with CHD.

TA-65MD, the only available human telomerase activator, has been shown to increase TL in human subjects. We hypothesize that maintaining and/or lengthening telomeres can reduce T cell immunosenescence, thus reducing their proinflammatory effects. Telomerase has also been shown to have telomere-independent properties in vitro, namely, a protective effect in cells under oxidative stress and an ability to regulate FMD in the human microvasculature.

The proposed pilot trial in older patients with CHD will provide findings not previously investigated outside in vitro or preclinical models, which will substantially enhance our understanding of telomerase activators in this population and their potential for benefit. The double-blind, randomized, placebo-controlled design of the TACTIC trial will provide the gold standard for evaluating signs of efficacy of TA-65MD. Should the results indicate reduced frequency of immunosenescent CD8+ T cells and improvements in TL as well as endothelial function, we will aim to follow up with a larger, multicenter efficacy trial in patients to determine if TA-65MD is beneficial in the treatment of CHD.

Acknowledgments

This trial would not be possible without the commitment and enthusiasm of clinicians, nurses (notably, Laura Thompson and Ben Ward), professionals, and patients within the Cardiology Department at The James Cook University Hospital, Middlesbrough, UK. Our thanks go to them and to the NCTU team. The trial is sponsored by South Tees Hospitals NHS Foundation Trust and funded by T.A. Sciences, Inc, New York, USA.

Authors' Contributions

IS conceived the idea for the study. IS, RM, HH, and AK co-designed the trial and secured funding from T.A. Sciences; together with DA, LM, and SD, they wrote the full TACTIC trial protocol. DA is the principal investigator at the recruiting center and leads recruitment and treatment of patients. BB is the clinical research fellow, recruits patients, undertakes assessments, and supports IS and DA. RM and HH provide methodological input and oversee NCTU activity. AK leads the statistical aspects and analysis. SD manages the trial, sets up the center, and performs monitoring. KB undertakes the assessment of blood samples at Newcastle University, including for the primary outcome. RA developed and validated the telomerase and TL assays needed for the trial and continues to advise in this capacity. AF is the core facility manager and has developed the validation of the FACS protocol (ie, primary outcome); he will continue to provide a quality assurance role in relation to the analysis of samples at

Newcastle University. This paper was drafted from the approved version of the protocol; all authors commented and amended drafts of the paper and approved the final version. All authors read and approved the final manuscript.

Conflicts of Interest

DA has received consultancy fees from Novartis, speaker fees from Astra Zeneca, and proctoring and speaker fees from Abbott Vascular. IS received an investigator-initiated trial grant from T.A. Sciences.

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Abbreviations

ACS: acute coronary syndrome
AE: adverse event
CAD: coronary artery disease

CAG: cycloastragenol
CANTOS: Canakinumab Anti-Inflammatory Thrombosis Outcomes Study
CHD: coronary heart disease
CMV: cytomegalovirus
DAMOCLES: Data Monitoring Committees: Lessons, Ethics, and Statistics
eCRF: electronic case report form
EudraCT: European Union Drug Regulating Authorities Clinical Trials Database
FACS: fluorescence-activated cell sorting
flow-FISH: flow cytometry-fluorescent in situ hybridization
FMD: flow-mediated dilation
GCP: Good Clinical Practice
GRAS: Generally Recognized As Safe
hsCRP: high - sensitivity C - reactive protein
ICH: International Conference on Harmonisation
IDMEC: Independent Data Monitoring and Ethics Committee
IL-1: interleukin 1
IMP: investigational medicinal product
ISRCTN: International Standard Randomized Controlled Trial Number
MACCE: major adverse cardiac and cerebrovascular events
MHRA: Medicines and Healthcare products Regulatory Agency
MI: myocardial infarction
MRC-5: Medical Research Council cell strain-5
NCTU: Newcastle Clinical Trial Unit
NHS: National Health Service
NSTEMI: non-ST elevation myocardial infarction
NT-proBNP: N-terminal fragment of the prohormone brain-type natriuretic peptide
PAT: Peripheral Arterial Tone (in EndoPAT)
PBMC: peripheral blood mononuclear cell
PCR: polymerase chain reaction
STEMI: ST elevation myocardial infarction
TA: telomerase activity
TACTIC: Telomerase ACTivator to reverse Immunosenescence in Acute Coronary Syndrome
TBARS: thiobarbituric acid reactive substances
TEMRA: T effector memory cells re-expressing CD45RA (CD45 expressing exon A)
TERT: telomerase reverse transcriptase
TL: telomere length
TRAP: telomeric repeat amplification protocol

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Protocol

The Impact of Previsit Contextual Data Collection on Patient-Provider Communication and Patient Activation: Study Protocol for a Randomized Controlled Trial

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Abstract

Background: Patient-centered care is respectful of and responsive to individual patient preferences, needs, and values. To provide patient-centered care, clinicians need to know and incorporate patients' context into their communication and care with patients. Patient contextual data (PCD) encompass social determinants of health and patients' needs, values, goals, and preferences relevant to their care. PCD can be challenging to collect as a routine component of the time-limited primary care visit.

Objective: This study aims to determine if patient-provider communication and patient activation are different for patient users and patient nonusers of an electronic health record (EHR)–integrated PCD tool and assess if the impact of using PCD on patient-provider communication and patient activation differs for Black and White patients.

Methods: We describe a randomized controlled trial of a prospective cohort of non-Hispanic White and Black patients who receive primary care services at a midwestern academic health care system in the United States. We will evaluate whether providing PCD through a consumer informatics tool enhances patient-provider communication, as measured by the Communication Assessment Tool, and we will evaluate patient activation, as measured by the Patient Activation Measure for PCD tool users and nonusers. Furthermore, owing to racial disparities in care and communication, we seek to determine if the adoption and use of the tool might narrow the differences between patient groups.

Results: The trial was funded in November 2017 and received local ethics review approval in February 2019. The study began recruitment in April 2019 and enrollment concluded in October 2019 with 301 participants. The analysis was completed in May 2020, and trial results are expected to be published in winter 2020.

Conclusions: Recently, there has been increased attention to the role of health information technology tools to enable patients to collaborate with providers through the sharing of PCD. The adoption of such tools may overcome the barriers of current EHRs by directly engaging patients to submit their contextual data. Effectively, these tools would support the EHR in providing a more holistic understanding of the patient. Research further supports that individuals who have robust digital engagement using consumer

informatics tools have higher participation in treatment follow-up and self-care across populations. Therefore, it is critical to investigate interventions that elicit and share patients' social risks and care preferences with the health care team as a mechanism to improve individualized care and reduce the gap in health outcomes.

Trial Registration: ClinicalTrials.gov NCT03766841; https://clinicaltrials.gov/ct2/show/NCT03766841

International Registered Report Identifier (IRRID): RR1-10.2196/20309

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KEYWORDS

physician-patient relations; consumer health informatics; patient participation; vulnerable populations; randomized controlled trial; patient-centered care; mobile phone

Introduction

Background

Over the past few decades, health care has been shifting from a paternalistic to patient-centered model that values patient engagement and shared decision making [1,2]. These values align with the patient-centered care model, where clinicians provide care that is tailored to the distinct needs of the patient. It is based on the development of respectful and dignified therapeutic relationships [3].

To provide patient-centered care, clinicians need to know and incorporate the patients' context into their communication and care with patients. Patient contextual data (PCD) encompass social determinants of health (SDH) [4] and further comprise patients' needs, values, goals, and preferences relevant to their care [5]. In the primary care setting, clinicians address most patients' health care needs through a sustained partnership with patients and within the context of family and community [6]. Therefore, care teams must have access to data about the patients' perspectives, values, and other contextual considerations to tailor patient-centered conversations and clinical decisions [1,6,7]. PCD can facilitate team-based care by enabling health care team members to build a rapport quickly and to connect with patients on a humanistic level [8].

Evidence suggests that connecting with patients can bolster patient activation. In a cross-sectional study, individuals at the highest level of activation (level 4) received relevant preventative cancer screenings, had 5 of 6 clinical indicators in the normal range, and did not engage in unhealthy behaviors (tobacco smoking and obesity) at statistically significantly higher rates compared with individuals in the lowest level of activation (level 1) [9]. A longitudinal study affirmed the results that indicated that people at the highest level of activation had significantly higher odds of guideline-concordant high-density lipoproteins and serum triglyceride levels, normal Patient Health Questionnaire-9 scores, not smoking, not being obese, having no Emergency Department visits, and having no hospitalizations in the 2-year follow-up period compared with people at the lowest levels of activation [9,10]. These outcomes translated to lower health care costs, with a projected 31% decrease in costs for people who were most activated (level 4) than those who were least activated (levels 1 and 2) [10].

Despite evidence indicating that connecting with patients improves patient outcomes and reduces health care costs [9,10], PCD are often not collected as a routine component of care [11].

A barrier to the integration of PCD is linked to the current limitation of electronic health record (EHR) systems in integrating and facilitating the retrieval of social risks and care preference data [12], even if collected as unstructured data within clinical notes. Clinicians face several limitations in terms of time [5,13] allocated to clinical visits and tools to gather a comprehensive understanding of their patients' needs, values, preferences, goals, and concerns. System-level barriers lead to missed opportunities to individualize care and act upon PCD that might have a substantial impact on patient outcomes and the experience of care [14].

Previous research has demonstrated that patients reveal more sensitive information via health information technology than during patient visits [15]. Studies show that unvoiced concerns and goals for care disproportionately relate to the patients' experience of illness [16,17], patients' expectations of treatment [18], or psychosocial concerns [17,19-21]. These *contextual errors* (ie, disregard of PCD in care planning) [14] are more costly to the health care system than biomedical errors (ie, guideline-discordant care) [11]. Conversely, when providers incorporate PCD into the care context, patients' engagement in their self-management and adherence to the agreed-upon care plan increases [22]. Furthermore, when the health care team collects and incorporates PCD during a visit, it facilitates rapport building and aligns patient and provider goals [5].

Strategies to Mitigate Disparities

Research indicates that there are ethnic and racial differences in the adoption of consumer informatics tools [23-26]. In a study of a national sample of US adults, ethnic and racial minorities were less likely to be invited to use a patient portal than ethnic and racial majority populations [27]. Furthermore, individuals who did not use a patient portal were more likely to be unemployed, receive Medicaid insurance, have less than a college-level education, did not have a regular health care provider, were male, and aged 65 years or above [26]. As patient portal usage has been shown to be associated with improved quality measures and is thought to contribute positively to patient safety, digital tools should be assessed for their capability to be adopted by a wide range of the population and to narrow, rather than grow, the gaps in care across groups [28].

Given that disparities exist in the adoption and use of consumer informatics tools [27,29,30], researchers must evaluate ways to reach vulnerable populations when testing new consumer information technologies. Current trends suggest that internet access is no longer the main cause of the digital divide [31].

Instead, some patients lack the knowledge, skills, and confidence in using technology [32]. Providers may be key to reduce differences in consumer technology use by inviting all patients to use the new technology, discussing privacy and security concerns and providing resources tailored to a low health literacy level, on use [26]. Additional strategies to reach the most vulnerable individuals and across racial groups include developers employing patient-centered design strategies such as a simple, clean, and aesthetically appealing interface [33]; incorporating patient education on how to use the technology [34]; and promoting the new technology in various ways [35]. Conceivably, introducing a new consumer informatics technology designed to improve patient activation and communication may not achieve the desired rates of adoption, unless health care team members actively promote and assist in the use of the technology [8,25,35,36].

Study Objectives

In this randomized controlled trial, we aim to evaluate the influence of PCD, collected using a consumer informatics tool, for previsit planning and routine clinical visit discussions with the health care team. The goal is to compare postvisit patient-provider communication and changes in patient activation among patient users and nonusers of the PCD tool, accounting for differences between non-Hispanic White and Black participants (hereafter White and Black). We will measure these constructs using 2 validated measures, the Communication Assessment Tool (CAT) [37] and the Patient Activation Measure (PAM) [38]. Furthermore, we will evaluate the impact by race by determining whether PCD could help mitigate any baseline differences in patient activation and postvisit patient-provider communication between White and Black patients.

We hypothesize that inviting patients directly to submit this information may help with several factors, including activation (patient ready to manage their health and care) and communication (helps prepare perspective and helps the clinician identify salient points).

The primary aims of this trial are to (1) assess the effects of using PCD on patient-provider communication (primary outcome) and patient activation (secondary outcome) and examine whether the effects are different for Black and White patients, accounting for age, gender, and other patient factors and (2) evaluate whether baseline measures of patient-provider communication and patient activation modify the effectiveness of PCD in improving either outcomes, accounting for age, gender, and other patient factors.

We have 2 outcomes of interest: (1) patient-provider communication measured using the CAT [37] and (2) patient activation measured using the PAM [38].

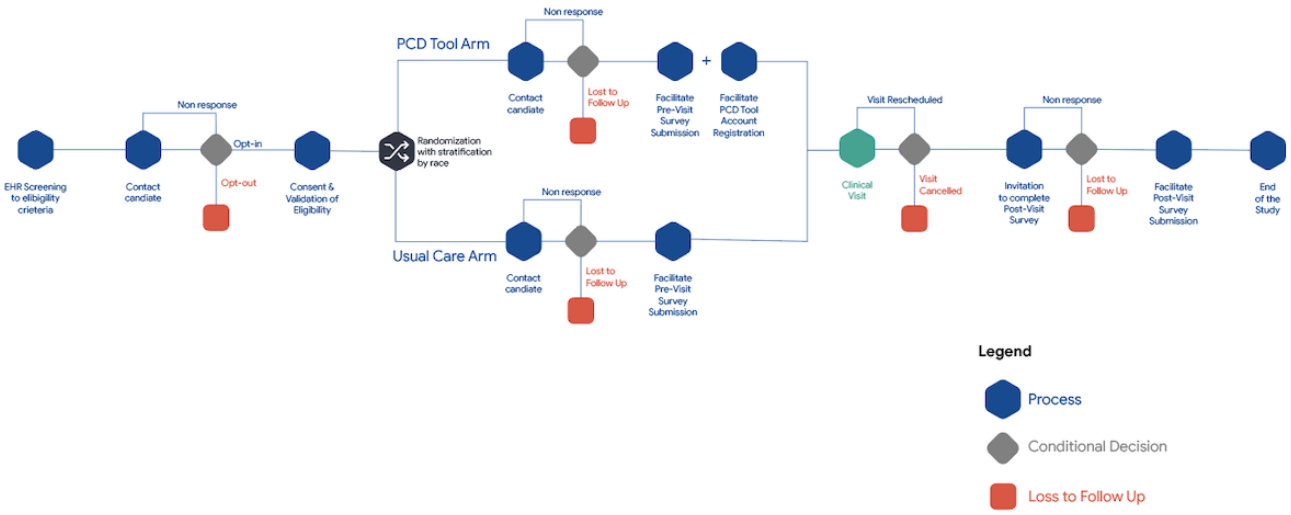
Methods

Study Design

This trial will assess the impact of incorporating PCD on patient-provider communication and patient activation of Black and White participants. The trial is registered at ClinicalTrials.gov (NCT03766841). The health network's ethics review board approved this trial (registered project PRO00031177). The study protocol adheres to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 [39] checklist (Multimedia Appendix 1).

Using an experimental study design, we will recruit a prospective cohort of eligible Black and White patients from primary care clinic sites randomized to intervention (invitation to use the PCD tool with facilitated enrollment) or usual care (invitation to use the PCD tool only) and administer questionnaires at baseline and after their primary care visit. The questionnaires assess the perceptions of visit communication and patient activation. The survey results will be adjusted for previsit measures of communication as the CAT [37] is only validated as a postvisit measure of patient-provider communication. Figure 1 presents the randomized controlled trial study design.

Figure 1. Randomized controlled trial study design.



Sample Size Determination and Randomization

An a priori power analysis was performed to estimate the required sample size using G*Power 3 [40,41] based on the study's primary outcome, the CAT [37]. These were conducted for the more straightforward two-sample *t* test procedure, as this is known to yield a conservative assessment of power. For a two-sided test at α=.05, a total sample size of 200 results in 80% power for a standardized effect size of 0.4 and 94% power for an effect size of 0.5. Increasing the sample size to 250 raises the power to 88% and 98%, respectively. A sample size of 250 provides 79% power to detect a standardized effect size of 0.35. To account for up to 20% potential dropout over time, we aim to enroll 300 participants (targeting 150 Black and 150 White participants). Once participants provide consent, REDCap (Research Electronic Data Capture) [40] will randomize them into 1 of 2 experimental arms: (1) PCD tool (ie, facilitated enrollment for PCD tool intervention) or (2) usual care (ie, email invitation only for PCD tool). We will use stratified random sampling to ensure equal representation of Black and White participants in each arm. Stratified randomization prevents an imbalance of racial representation between arms.

Randomization of Study Participants

Allocation Process

An allocation table was created using R to develop a block randomization scheme to balance arms and stratification by race. The block randomization scheme was then incorporated into the REDCap [40] system. Randomization is stratified by race in a 1:1 ratio, ensuring that we oversample Black participants based on population demographics. Blinding does not occur for either the participant or the study team. Participants are invited to join a communication study but are not told whether the study will focus on their use of the PCD tool.

Study Population

A total of 300 adults (≥18 years) with established primary care providers (ie, at least one visit in the previous 12 months with the same provider) from 2 academic and community-based primary care clinics of the Medical College of Wisconsin in Milwaukee, Wisconsin, United States, will be recruited for the study.

Inclusion Criteria

Eligible participants are individuals (1) aged 18 years or above, (2) who self-identify as non-Hispanic White or Black, (3) who speak and understand English, (4) who are willing and able to give informed consent, and (5) who at the time of the study enrollment period have an upcoming visit (1-4 weeks away), (6) whose appointment at one of the academic medical center's primary care clinics, and (7) whose appointment is with an established provider (at least one previous appointment with the same provider within the last 12 months).

Recruitment

We will use consecutive convenience sampling to select every person who meets the inclusion criteria based on weekly EHR data reports. This sampling procedure minimizes selection bias (ie, volunteerism) [42]. Using the institution's local informatics tools [43], we estimated the number of unique patients seen at the eligible clinics in 2016 to be 5200 Black and 13,750 non-Hispanic White patients. Restricting to unique patients with a preventive service encounter in 2016 (a conservative estimate as it excludes patients for whom a preventive exam was not billed, which includes most Medicare patients), there remain over 980 Black and 3725 non-Hispanic White patients who are eligible to participate.

We will contact the participants through a mailed letter or email. The invitation to participate describes the study as "a study to better understand and improve patients' experiences of care and communication with their doctors." Research staff will contact eligible participants by phone up to three times to answer questions, encourage participation, and facilitate the completion of the baseline survey. Recruitment will continue until we reach our target sample size of 300. We will collect the survey data using the REDCap system [44] hosted at the academic medical center.

Informed Consent

The informational letter participants receive as part of the informed consent process can be found in Multimedia Appendix 2.

Intervention

EHR-integrated PCD Tool

The Froedtert and Medical College of Wisconsin health network partnered with a digital health company, PatientWisdom Inc, to develop a digital web-based platform to engage with patients ahead of visits. After creating an account on the platform, each participant would be able to provide information about themselves and their situations (ie, PCD) as well as their agenda for the next visit through a mobile and web interface.

The PCD tool is a web-based application running on a Health Insurance Portability and Accountability Act–compliant platform. It has a responsive design that allows for ease of use across a range of devices, from desktops to tablets and smartphones. The tool was codeveloped by the health network, its patients, its clinicians, and an PatientWisdom, Inc. The consumer informatics tool draws upon deep experience and evidence in patient communication [37,45]. The tool invites patients to share *stories* about themselves, their health, and their care. For example, in the *My Self Story* section, patients share what they want their health care team to know about them as individuals, what brings them joy, and about the pressures in their life such as social and personal determinants of health. This section also includes the patient's health-related priorities and goals and the barriers they experience in achieving them. In addition, in the *My Health Story* section, patients share questions or concerns they want to discuss with the care team, rate their health and provide reasons for the rating, and provide a perspective on how identified health issues affect their lives.

Furthermore, patients identify their preferences toward shared decision making and identify people who support them with health care decisions. Patients can access the application directly through a web address or through a drop-down menu embedded in the patient portal that provides a single sign-on experience for the patient. The latter process makes a direct linkage between

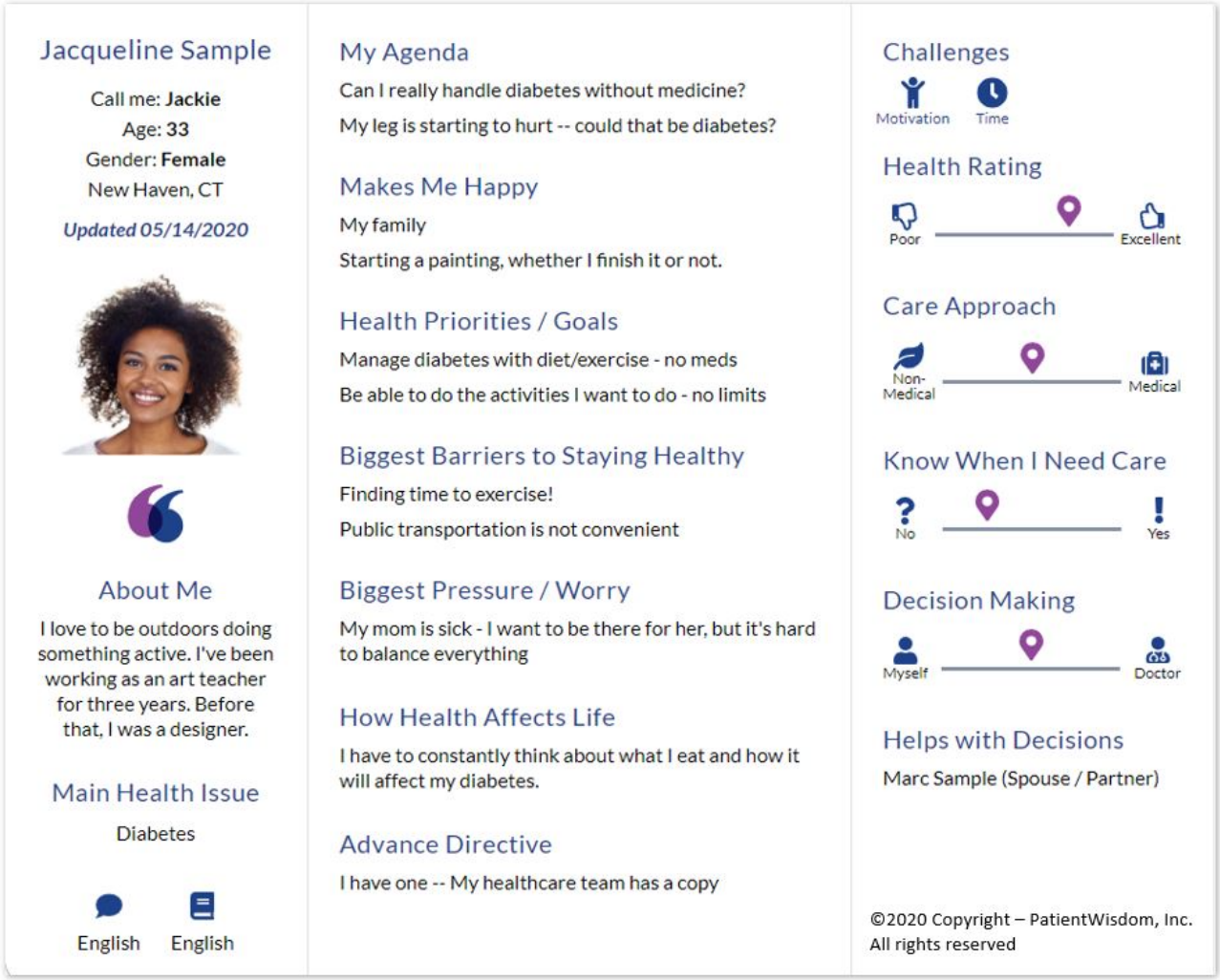
the patient and the patient in the EHR. If the patient does not use the patient portal, a statistical matching algorithm links the accounts between the PCD tool and the EHR. After the linkage occurs, clinicians can click on an activity tab within the EHR to view a one-screen summary of the patient's responses. From preliminary data, average engagement with the tool by patient PCD tool users is approximately 7 min per encounter.

EHR Integration

The EHR-integrated PCD tool synthesizes information from the *My Self* and *My Health* stories to create an at-a-glance one-screen view (Figure 2; PCD tool one-screen summary) of the patient, their context, and what is relevant to them. The one-screen summary includes content to facilitate a personal connection and to efficiently grasp goals of care, agenda items, barriers, SDH, styles, and preferences. The 1-page summary highlights elements that the patient recently updated. From preliminary data, clinicians view the summary for approximately 1 min.

As the developers designed the tool to be asynchronous, they established an alert process to flag text and notify clinicians of critical patient data (eg, thoughts of suicide, domestic violence, or distressing symptoms) to guarantee timely interventions [5]. There are plans to transition the alert process to natural language processing once enough PCD are gathered for deep learning.

Figure 2. Patient contextual data tool one-screen summary.



PCD Tool Arm

After completion of the previsit survey, all participants in the intervention group will receive an email with a link to the PCD tool for participants to complete their profile. Participants are given the option to complete their PCD profile independently or with assistance from one of the research staff. Providing the participant with options to complete their PCD profile ensures that the participant has access to the internet and a device. Facilitating the enrollment process may also overcome the current rates of adoption and use of the tool (4.7% in 2018) by being responsive to participants' varying degrees of computer literacy and technical skills.

For participants who do not have an email address and decline to sign up for one, a paper survey will be used to collect the PCD and share them with the health care team at the time of the appointment. Although completion of a paper form loses some of the elements of the trial (PCD not integrated into the EHR), it decreases the chances of adding bias in the study as Blacks are less likely than Whites to have an email account [32,46].

Enrollment Process for PCD Tool Facilitation

The facilitation enrollment process includes a description of the PCD tool, followed by the study team member either assisting the participant in registering a PCD tool account using the link to the PCD tool site sent by email or describing how to register a PCD tool account through the patient's portal. Next, the study team member will review the types of *stories* to share, in the domains of (1) information about me, (2) issues related to my care, (3) my upcoming visit agenda, and (4) barriers to care, to highlight all of them as important pieces of data. In addition, the study team member will share how to upload a picture to the profile. After completing the instructions, the study team member will share that the completed profile would then be available to the care team. The participant can then view how their profile would appear in their EHR via the one-screen summary.

The research team member will document the type of PCD tool facilitation (ie, email link only, over the telephone, or in person) for each participant and take field notes of each facilitation experience. Approximately 1 week before the primary care visit, the research staff will recontact the participant either by telephone or email up to three times. The research staff will thank the participant for being part of the study and inquire if they have questions regarding completing or updating their PCD tool profile. Research staff will also remind the participant to complete the profile, if it is not yet finished.

Usual Care Arm

Participants randomized to the usual care arm will complete their previsit survey, scheduled primary care visit, and postvisit survey. The only information regarding the PCD tool they receive before their visit is the email sent automatically by the EHR system to all patients at the academic medical center to create or update their PCD account 1 week before their appointment. For participants who did not have a previsit survey completed at least five days ahead of the appointment, a study team member will give a call to remind the participant to complete the survey as soon as possible. For participants who indicate a preference to complete the previsit survey over the telephone or in person, the study team member will read the survey items verbatim and complete the survey in REDCap.

For both arms, after the scheduled primary care clinic visit occurs, participants will receive up to 3 email reminders to complete the postvisit survey. A study team member will give a call to remind the participant to complete the postvisit survey if it is not completed after the third email reminder. For participants who indicate a preference to complete the postvisit survey over the telephone or in person, the study team member will read the survey items verbatim and complete the survey in REDCap.

Data Collection

We will use self-reported surveys to assess the differences in patient-provider communication and patient activation between the PCD tool and usual care arms and by race (Black and White). The primary outcome measure is patient-provider communication assessed using the CAT [37] after the visit. The 15-item measure is unidimensional and has high internal consistency (Cronbach α=.96), with readability at or below an eighth-grade level [37]. The psychometric properties of CAT were tested in a diverse sample. The testing revealed that the instrument has content and construct validity and reliably [37] measures patients' perceptions of physicians' interpersonal communication skills. We will examine individual items and the proportion of items with top ratings. The CAT was designed to be administered directly following a visit and is not yet validated in a retrospective context. Therefore, we will use the Clinician and Group Consumer Assessment of Healthcare Providers and Systems (CG-CAHPS) survey [47,48] communication composite questions validated for patients' perceptions of communication with their provider within the past 12 months as the baseline communication measure. The outcome will be the CAT adjusted for the baseline CG-CAHPS score.

We will use the 13-item PAM [38] to assess changes in the secondary outcome and patient activation, examining the change in pre- and postvisit assessments. Conducted with a nationally representative sample, psychometric testing revealed that the 13-item PAM questionnaire yielded a strong Rasch person reliability score between .85 (real) and .87 (model), and the Cronbach α value was acceptable at .87 [38].

We will collect the following independent variables in the previsit survey: CG-CAHPS communication composite [47], Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health [49], health literacy [50], technology use or technology acceptance [51], and sociodemographic characteristics. We will measure previsit patient-provider communication using the communication composite of the CG-CAHPS survey [48]. The CG-CAHPS communication composite has high internal consistency (Cronbach α=.89) [47], which was determined using a nationally representative sample of over 21,000 patients from 450 US practice sites. We will assess participants' perceptions of their global health using the PROMIS 10-item Global Health Short Form, which includes scores on global physical health and global mental health. The PROMIS 10-item Global Health Short Form scales had internal consistency reliability coefficients of 0.81 for global physical health and 0.86 for global mental health in a large national survey [49]. Technology use or technology acceptance will be collected using the Health Information National Trends Survey 5, Cycle 1 [51]. Participants will report health literacy using a validated one-item tool [50]. Sociodemographic characteristics and other hypothesized predictors of the outcome measures include income, age, sex, gender identity, health insurance status, educational attainment, number and type of chronic conditions, and length of relationship with primary care provider (in months or years).

We will monitor the use of the PCD tool in 3 ways. First, we will assess whether those in the PCD tool arm completed their profile before their appointment. Second, for participants in the usual care arm, we will determine if they created a profile after they entered the study, as all patients in the academic medical center have access to the PCD tool. Third, we will assess whether any of the care team members reviewed the participant's PCD tool profile within one day before the appointment and on the day of the appointment. Figure 3 displays the Randomized

Controlled Trial Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [39] including an overview of study time points, intervention, and assessments of the randomized controlled trial.

Figure 3. Randomized controlled trial Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT).

	Study Period					
	Enrollment	Allocation				
Timepoint	**$-t_1$**	**0**	**t_1**	**t_2**	**t_3**	**t_4**
Enrollment:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
Intervention:						
PCD tool			Baseline Survey	PCD Tool Via Facilitated Enrollment	Primary care visit	Post-visit Surv
Usual care			Baseline Survey		Primary care visit	Post-visit Survey
Assessments:						
Gender			X			
Age			X			
Race			X			
Ethnicity			X			
Sex			X			
Marital status			X			
Employment status			X			
Health insurance			X			
Household income			X			
Difficulty paying bills			X			
Education			X			
Health literacy			X			
Technology use/ acceptance			X			
PROMIS Global Health			X			
Length of time with provider			X			
CG-CAHPS			X			
Patient Activation Measure			X			X
Communication Assessment Tool						X
PCD tool perceived ease of use, usefulness, and acceptance						X
PCD tool use by clinician type						X

Note. The SPIRIT figure displays an overview of study time points, intervention, and assessments of the randomized control trial. PCD patient-generated contextual data, CG-CAHPS clinician group consumer assessment of healthcare providers and systems

Data Management

The research team will use REDCap for data management [44]. This system is a secure, web-based application designed by Vanderbilt University to support data collection for research. It provides data validation, audit trails, and automated export procedures to a variety of statistical packages. As necessary, branching logic and calculated fields will be created in the system to support data entry.

Data Monitoring

The data monitoring committee comprises the study team, the PCD tool's implementation manager, and the Department of Medicine Safety Committee (DMSC). This pragmatic trial is of low risk, but several monitoring processes are in place to protect the participants. The participants are provided with the study team's phone number and email address. Participants also have contact phone numbers of members of the ethics review board and can notify the principal investigator (PI) of any harm, which will be reported to the local institution. If a participant shares concerning data (eg, thoughts or actions of self-harm, domestic violence) in their PCD tool profile, the provider is alerted and contact with the participant is initiated. The study team will not conduct interim analyses because of the low-risk nature of the trial. There is an independent process for the DMSC to review all PCD tool data for quality in each quarter.

Ethical Considerations

The academic health network's ethics review board approved the study before enrollment. The study PI will report changes to the protocol to ClinicalTrials.gov, local ethics review board, and all study team members. All study personnel have completed training on the protection of human subjects in research. Data will be stored on a secure server with physical, technical, and administrative access controls using the academic health system–approved REDCap software. Remote access is available over a secure network via encrypted connections to password-authorized users. The media will be kept in locked file cabinets in locked offices. Files with participant identifiers will be stripped of identifiers as soon as they are no longer needed. The study staff have no conflicts of interest. A subsidiary of the affiliated health system has an investment in the company that owns the PCD tool. However, the study staff are not directly employed by the health system nor have any financial ties to the company. There are no provisions for ancillary or postcare of the trial because of the nature of use of the PCD tool, which is currently available to the health system's patients.

Analysis

The trial will evaluate the differences between the arms for change in PAM scores [38] and the CAT score (a postvisit measure) [37], adjusting for the CG-CAHPS score (a previsit measure). The research team will also assess differences in pre- and postvisit patient activation and postvisit patient-provider communication by race. Our primary analysis is an intention-to-treat (ITT) analysis, where every randomized participant is analyzed in the group to which they were randomly assigned [52,53]. Chi-square tests for categorical variables and independent sample *t* tests for continuous variables will be used to examine the differences between the groups at baseline and postvisit. Descriptive statistics (means and standard deviations) will be conducted for the following variables: age, CG-CAHPS communication composite score [47], and PROMIS 10-item Global Health Short Form [49]. Frequencies will be calculated for sex, gender identity, education, marital status, employment status, income, health insurance coverage and type, difficulty paying bills, health literacy, internet use, internet access, internet access location, and internet access device. We will also extract data from each participant's EHR to calculate their Charlson Comorbidity Index [54] as a measure of morbidity. Previsit assessment of communication using CG-CAHPS [47] as a control variable and postvisit assessment of communication using the CAT [37] will be tested within and between groups using linear regression, controlling for covariates. A linear regression model will be used to determine the factors that predict changes in patient-provider communication and patient activation, controlling for covariates.

However, we expect that there will be some crossover and noncompliance between arms. For example, some individuals randomized to the PCD tool arm may not complete a profile, and some individuals not randomized to enroll in the PCD tool may create a profile. To overcome this limitation, we will conduct additional analyses that account for noncompliance and estimate the effect of the treatment-on-the-treated (TOT) instead of the ITT [55,56]. TOT is sometimes referred to as the local average treatment effect or as a *per-protocol* analysis. We will identify this using a two-stage least squares regression [57,58]. The first stage of the model estimates whether a person used the PCD tool during the follow-up period.

The second stage will identify the causal impact of using the PCD tool on outcomes (patient activation and patient-provider communication). To do this, we will model the predicted use of the PCD tool from stage 1 in the stage 2 model and use the results of this coefficient to interpret how the PCD tool impacts patient activation and patient-provider communication.

A missing value analysis will be conducted on the final data set to determine whether data were missing completely at random, missing at random, or missing not at random [59,60]. To reduce the likelihood of missing data biasing our results, we will use multiple imputation by chained equations to fill in missing data stratified by race [59]. The imputation algorithm will include participant demographics and clinical characteristics. Multiple imputation has been increasingly applied to clinical research to address the common problem of incomplete data sets [60].

For all aims, statistical analysis will be completed using SAS [61] procedures GLM and MIXED to assess and account for possible provider and center heterogeneity. A P value of $<.05$ is considered statistically significant.

Dissemination

We intend to write and publish 2 manuscripts (corresponding to each outcome, the CAT and the PAM), adhering to the International Committee of Medical Journal Editors [62] authorship recommendations. In addition, we will communicate the study results to the academic health system leadership, primary care clinics, developer of the tool, and the medical community.

Trial Status

The study on the impact of PCD on patient-provider communication and patient activation began recruitment on April 1, 2019. The trial ended recruitment on October 18, 2019.

Results

The trial was funded in November 2017 and received local ethics review approval in February 2019. The study began recruitment in April 2019 and enrollment concluded in October 2019 with 301 participants. Analysis was completed in May 2020, and trial results are expected to be published in winter 2020.

Discussion

Role of Consumer Informatics

There is increasing attention on the role of health information technology and digital health tools to enable patients to collaborate with providers by sharing and acting upon PCD [12,63-70]. Adoption of consumer-facing informatics tools may overcome the barriers of current EHRs by directly engaging patients to share PCD. Moreover, with the advent of application programming interfaces and the increasing level of

interoperability of EHR systems, these consumer applications can integrate PCD information into current EHR systems to make the data available for use by clinicians and health care teams [1,71]. In particular, consumer informatics tools that gather and share PCD are hypothesized to improve communication [21] and health outcomes [72,73]. Effectively, these tools would support the EHR in providing a more holistic understanding of the patient.

In an earlier study [8], digitally engaged patients reported that the completion of their profiles in a consumer informatics tool (ie PatientWisdom, Inc.) promoted reflection of their health goals, challenges, and priorities. The reflection led to actions toward goal attainment and targeted conversations with their health care team about issues important to them [8]. Research further supports that individuals who have robust digital engagement using consumer informatics tools have higher participation in treatment follow-up and self-care [74,75]. When care goals were aligned, racial and ethnic minority populations experienced improvements in patient-provider communication and decision quality outcomes similar to racial and ethnic majority populations [25,76]. Therefore, it is critical to understand whether interventions that elicit and share patients' social risks and care preferences with the health care team serve as a mechanism to improve individualized care and lessen the gap in health outcomes.

Summary, Strengths, Limitations, Contingency Strategies, and Alternative Designs

The clinical trial will provide crucial empirical evidence on the effects of a consumer informatics tool that elicits and aggregates PCD for use in the clinical exchange of patient-provider communication and patient activation across populations. The study will occur within the most racially segregated metropolitan area in the United States, where racial disparities in health and health care represent a significant public health concern [77-80]. The study sample may not reflect the population or the complex contextual issues associated with the area.

We acknowledge the following limitations and significant threats to the study and present contingency strategies. This research study will occur within 1 academic medical center, which may limit the generalizability of the results. To mitigate this limitation, we will recruit participants from various academic and community primary care clinics with different staff, providers, milieu, and the composition of patients who receive care. The participants in this study will be Black and White and limited to individuals who can speak English. This inclusion criterion excludes other diverse populations. This limitation is because of the population of patients who are served at the academic medical center. To reach equal racial representation of participants, we will oversample Black primary care patients. Recruitment difficulties for participation may occur. We employ several recommended strategies to recruit Black populations into this trial but lack other strategies such as community involvement and informational sessions [81]. Furthermore, the study may be threatened by volunteer bias, where the participants' characteristics or outcomes differ from those of nonparticipants [41]. An efficacious strategy to improve participant recruitment and retention is to compensate individuals for their time [41]. Participants will receive a modest financial incentive for participation in this research project. The incentive is US $25 for each survey completed. The study team has also allocated substantial time and resources for personalized telephonic or in-person contact during recruitment, retention, and follow-up procedures. Researchers have successfully used these strategies to recruit and retain historically disenfranchised populations in clinical trials [41].

We also considered the alternative design of an efficiency trial with its advantages of high internal validity [53]. Although there are methodological advantages to this design, the real-life variability of clinical practice precludes the strict adherence to a study protocol mandated in an efficiency trial. Therefore, we chose a pragmatic clinical trial with somewhat diminished internal validity but a high degree of external validity of the results, which is valued in implementation research [53].

Study Design Innovations

Health care stakeholders, clinicians, and patients increasingly call for the evaluation of clinically relevant interventions that are tested in heterogeneous clinical settings with the inclusion of diverse study participants [56,82]. In this clinical trial, we will test an intervention (PCD tool) that is deployed across an academic health network. We focus on understanding the differences by use, adjusting for problems with bias and self-selection of users for the PCD tool. The study design intends to overcome self-selection bias by creating randomization to treatment using various facilitation processes to improve the usage of the tool beyond its baseline. In addition to the ITT analysis, typical in pragmatic trials [55], we will conduct a TOT analysis [57,58] to model estimates of whether a participant used the PCD tool in the follow-up period and then identify the causal impact of using the PCD tool on outcomes (patient activation and patient-provider communication). In this study, the TOT analysis will adjust for participants' nonadherence to the group assignment, a common occurrence in pragmatic trials [56].

Conclusions

When patients' preferences and life circumstances drive health care decisions, their quality of involvement in their care improves [9,83-85]. PCD are essential information that, when known and incorporated, may promote the development of a person-centered plan for care [14]. Therefore, interventions that test these relationships must be explored to understand how to optimize individuals' involvement in self-care. Researchers must also investigate whether the outcomes differ between Black and White patients who experience different social, political, and economic injustices that affect health [86].

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Checklist.
[DOCX File , 35 KB - resprot_v9i9e20309_app1.docx]

Multimedia Appendix 2
Randomized controlled trial informed consent.
[DOCX File , 13 KB - resprot_v9i9e20309_app2.docx]

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Abbreviations

CG-CAHPS: Clinician and Group Consumer Assessment of Healthcare Providers and Systems
EHR: electronic health record
HHS: US Department of Health and Human Services
HRSA: Health Resources and Services Administration
PAM: Patient Activation Measure
PCD: patient contextual data
SDH: social determinants of health

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Protocol

Guided Self-Help Behavioral Activation Intervention for Geriatric Depression: Protocol for Pilot Randomized Controlled Trial

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Abstract

Background: Aging is a social concern. The increased incidence of depression in older populations in China poses a challenge to the health care system. Older adults who are depressed often suffer from a lack of motivation. Behavioral activation treatment, an evidence-based guided self-help treatment, is effective in reducing anhedonia and amotivation in depression; however, the efficacy of guided self-help behavioral activation in older adults with depression is not yet known.

Objective: The aim of this study is to pilot a self-help guided intervention for the treatment of depression in older adults.

Methods: This study has been designed as a pilot randomized controlled trial with inpatients (n=60; to be randomly allocated 1:1) between the ages of 60 and 70 and who have major depressive disorder. Patients attending clinical psychological clinics at the Mental Health Center of Chongqing will be randomized to either receive guided self-help behavioral activation (intervention) or to be on a 6-week waiting list (control). Participants in the treatment group will receive 6 sessions of guided self-help behavioral activation delivered over the telephone. The waiting list control group will receive the intervention after a period of 6 weeks. Exclusion criteria will be individuals who are at significant risk of harming themselves or others, who have a primary mental health disorder other than depression, or who have an intellectual disability that would hamper their ability to participate in the intervention. Effects of the treatment will be observed using outcomes in 3 domains: (1) clinical outcomes (symptom severity, recovery rate), (2) process variables (patient satisfaction, attendance, dropout), and (3) economic outcomes (cost and resource use). We will also examine mediators of outcomes in terms of patient variables (behavioral activation or inhibition motivation). We hypothesize that guided self-help behavioral activation will have a beneficial effect.

Results: The study was approved by the research ethics committee of the Mental Health Center of Chongqing in November 2019. As of July 2020, recruitment had not yet begun. Data collection is expected to be completed by December 2020. Data analysis is expected to be completed by June 2021. Results will then be disseminated to patients, to the public, to clinicians, and to researchers through publications in journals and presentations at conferences.

Conclusions: This will be the first study in China to investigate guided self-help interventions for patients who are older adults and who are depressed, a group which is currently underrepresented in mental health research. The intervention is modular and adapted from an empirically supported behavioral activation treatment for depression. The generalizability and broad inclusion criteria are strengths.

Trial Registration: Chinese Clinical Trial Register ChiCTR1900026066; http://www.chictr.org.cn/showprojen.aspx?proj=43548

International Registered Report Identifier (IRRID): PRR1-10.2196/18259

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KEYWORDS

psychiatry; clinical; psychology; geriatric depression; guided self-help; behavior activation; behavior inhibition; behavior treatment

Introduction

With the increase in life expectancy and low fertility rate, the health of the aging population has become a social concern. The World Health Organization defines older adults as individuals over 65 years of age (or over 60 years of age, in some instances). Chongqing is among the provinces of China that have a rapidly aging population. According to the data from China's 2010 population census, the percentage of the population over 65 years of age (14.51%) is higher in Chongqing than those in other provinces in China. In 2020, the population that is 65 years and older in Chongqing is predicted to grow to approximately 3.93 million [1].

With the increase in the aging population, depression in older adults has become the most important public health issue and can significantly increase the total cost of medical services [2]. Geriatric depression specifically refers to primary depression that first occurs after the age of 60 and which cannot be explained by physical symptoms or other organic diseases [3]. In a 2006 nationwide survey, among urban and rural older adults who were assessed with 15-item Geriatric Depression Scale, 13.6% and 25.5% demonstrated moderate or severe depressive symptoms, respectively [4]. Specifically, the aggregate prevalence of depression in the central and western regions (33.7%) was significantly higher than that in the eastern regions (19.1%) of China (measured with Geriatric Depression Scale or Center for Epidemiologic Studies Depression scale) [5]. Among older adults in Chongqing, 24.3% had depressive symptoms (a score greater than 11 on the 30-item Geriatric Depression Scale) [6]. People with chronic diseases, with physical disabilities, and who were living alone, as well as women and older adults in rural areas were more likely to suffer from depression [7].

Evidence-based treatment of geriatric depression mostly focuses on pharmacological treatment [8]. Recent reviews support the efficacy of psychosocial interventions in the acute treatment of geriatric depression [9-11]. A systematic review of randomized controlled trials revealed that behavioral therapy in older adults with depression had comparable effectiveness to those of alternative psychotherapies, such as cognitive therapy or brief psychodynamic therapy [12], as well as to that of antidepressant medication [13]. Behavioral activation is a standalone behavioral therapy developed for the treatment of depression which aims to increase positive reinforcement (such as obtaining a sense of pleasure and control) after the patient engages in antidepressant behavior (such as completion of scheduled activity or active social engagement), which then improves depression symptoms [14]. The monitoring and scheduling of activities are common components of behavioral activation treatment [15]. Activity scheduling, as the effective component of behavioral activation, when compared with controls showed significant effect size [16].

The brevity and simplicity of training and supervision, as well as multiple delivery modes (individual or group, face-to-face, or mobile-based) of behavioral activation may allow greater access, including in primary care and home settings. Currently, depression in older adults is treated mainly in primary care or home settings [17] and is often inadequately treated [8]. As mental health telehealth service matures, self-help treatment can be performed regularly under the guidance of therapists by using mobile technology such as smartphones and the internet. Compared to drug treatments, patients are more inclined to receive guided self-help therapy and psychotherapy [18]. Furthermore, according to the National Institute for Health and Care Excellence guidelines [19], guided self-help interventions delivered without human support or guidance have supporting evidence (degree II), and developing positive activities (the key component of behavioral activation) have supporting evidence (degree I) [20]. Moreover, self-administered behavioral activation interventions based on a self-help book [21] have significantly decreased mild or subthreshold depressive symptoms in late-life individuals (age range 65 to 89) [22]; however, there has still been no report on the implementation of guided self-help behavioral activation interventions for inpatients with geriatric depression. The inpatient group was selected because medical staff have received training to provide professional and systematic psychotherapy (such as cognitive behavior therapy or psychodynamic therapy) and drug intervention, which would not be accessible in the community.

Methods

Overview

A guided self-help behavioral activation intervention will be used to implement psychological education about depression and treatment plans for patients with geriatric depression; the behavioral activation intervention app developed by our research group will be used for monitoring and scheduling pleasurable activities. The Geriatric Depression Scale combined with the Behavioral Activation and Behavioral Inhibition scale will be used to investigate the efficacy of behavioral activation on inpatients with geriatric depression.

Participants

A total of 60 older adults who meet the diagnostic criteria of geriatric depression will be recruited. Participants will be randomly assigned to either the intervention group or the control group, with 30 individuals in each group.

Inclusion criteria are patients conforming to the ICD-10 diagnostic criteria (F32: Major depressive disorder, single episode); residing in Chongqing for more than 6 months; who can communicate barrier-free and are able to complete questionnaires independently or with assistance; who are aged from 60 to 70 years, with an education level of junior high school or above; and who frequently use smartphones (to be able to receive and check text messages and to be able to perform psychological assessments using a simple visual scale).

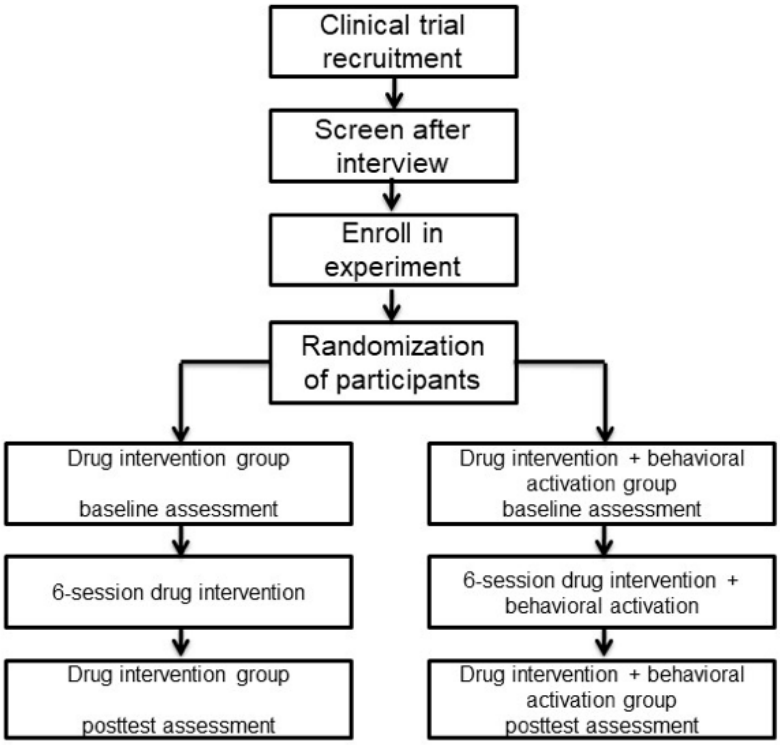
Exclusion criteria are patients with severe physical illness and organic brain diseases; with confirmed schizophrenia spectrum,

psychoactive substance use, or significant neurodevelopmental disorders; with bipolar disorder; with a recent history of severe infection and fever; with severe suicidal tendencies; or with other conditions deemed as not suitable for inclusion after evaluation by researchers.

Study Design

The behavioral activation group and the control group will both receive selective serotonin reuptake inhibitor treatment, conventional care, and health education; however, behavioral activation therapy will only be used in the intervention group, will be in accordance with the behavioral activation treatment for depression manual [23], and will be performed for 40 to 50 minutes twice each week for 3 weeks (Figure 1). During the intervention, the therapist provides education and behavioral skills for geriatric depression. Additionally, the behavioral intervention software that we developed will be used to assess changes in depression symptoms, to assess psychological mediators, and to monitor the completion of behavioral activation tasks.

Figure 1. Study design of guided self-help behavior activation intervention for geriatric depression.



Treatment Sessions

The intervention is designed as 6 treatment sessions. The first session provides psychological education about depression. The treatment concept and the status and importance of daily monitoring in the treatment process are introduced to participants. The second session involves a review of the previous treatment course to introduce the value and concepts of the activity plan. In different life domains (such as family relationships, learning and work, leisure activities, and hobbies and interests), participants and therapists are inspired through suggestion and writing tasks to list a series of activities that they feel are valuable and enjoyable. The activity schedule is listed together with therapists to allow participants to obtain maximum positive reinforcement in life. During the third to fifth sessions, the treatment concept is constantly reviewed and revised. Participants are asked to make an activity to-do-list using the activity schedule. The sixth session is used to discuss the completion of the treatment, evaluate treatment progress, and teach participants to prevent recurrence using the knowledge and skills learned from treatment [24] (Table 1). After each intervention, the behavioral activation intervention software that we developed assists individual self-learning (psychological knowledge of depression and behavioral activation), establishment of an activity schedule, and monitoring of daily emotional changes. Each session uses the self-rating scale to monitor depression symptoms and motivation changes in patients.

Table 1. Establishment of the treatment courses of behavioral activation therapy.

Course	Content	Tasks
1	1. Understanding basic knowledge of depression 2. Understanding treatment principles 3. Mastering principles and methods of the daily activity monitoring table	1. Finishing the daily activity monitoring table
2	1. Reviewing treatment principles 2. Reviewing the daily activity monitoring table 3. Discussing and solving issues in treatment 4. Discussing life domains and activities that are valuable to visitors	1. Finishing the daily activity monitoring table 2. Finishing life domain value assessment and the activity list
3	1. Reviewing the daily activity monitoring table 2. Reviewing the life domain value assessment and the activity list 3. Choosing and sorting activities that need to be reinforced	1. Finishing the daily activity monitoring table 2. Reviewing and improving life domain value assessment and the activity list 3. Reviewing and improving the activity sorting table
4	1. Reviewing the daily activity monitoring table 2. Reviewing the activity list 3. Signing the behavior agreement 4. Planning daily activities that need to be finished next week	1. Finishing the daily activity monitoring table 2. Supplementing and improving the behavior agreement
5	1. Reviewing the daily activity monitoring table 2. Reviewing the behavior agreement 3. Planning daily activities that need to be finished next week	1. Finishing the daily activity monitoring table 2. Supplementing and improving the behavior agreement
6	1. Reviewing the daily activity monitoring table 2. Planning daily activities that need to be finished next week 3. Preparing to finish up	1. Finishing the daily activity monitoring table 2. Supplementing and improving the behavior agreement

Quality Control

Study participants will be selected strictly according to the inclusion and exclusion criteria. Medical care staff with patience, technique, and strong responsibility will be chosen for performing guidance. They will receive uniform, rigorous training before performing guidance. Attention will be paid to communication skills and to the protection of patient privacy. The data input and review system will be established to ensure the accuracy of data input and analysis.

Health Outcomes

The Geriatric Depression Scale [25] is a self-rating depression scale specifically developed for older adults. This instrument includes a total of 30 items. The statistical indicator of this scale is the total score. A total score of 0-10 points indicates no depression symptoms, 11-20 points indicates mild depression symptoms, 21-25 points indicates moderate depression symptoms, and 26-30 points indicates severe depression symptoms. The Behavioral Inhibition System and Behavioral Activation System scale [26,27] has 20 items and is divided into 2 systems: the behavioral inhibition system and the behavioral activation system (including 3 dimensions: reward response, drive, and fun seeking). Each item is assessed using a 4-point Likert scale ranging from “completely agree” to “completely disagree.” The Cronbach α (for all dimensions) ranges from 0.66-0.76 [27]. The reliability after 2 months is approximately 0.59-0.69 [27].

Efficacy Outcomes

After 6 months, at follow-up, the recurrence rate will be evaluated using the Clinical Global Impression scale [28]. The Treatment Emergent Symptom Scale [29] will also be used to evaluate side effects.

Statistical Analysis

This study will focuses on clinical outcomes in terms of reduction of symptom severity and on motivation (behavioral activation or inhibition) as mediators, as well as descriptive statistics of recovery rates. The process variables, including patient satisfaction, attendance, dropouts, will be reported. The cost-effectiveness of the intervention will be reported in terms of cost and resource use.

Independent and paired *t* tests will be performed using SPSS software (version 22.0; IBM Corp) to investigate the improvement effect in depression symptoms from the behavioral activation intervention. Amos software (version 17.0; IBM Corp), combined with the mediation effect model, will be used to investigate the mediating effect of the behavioral activation inhibition level on the improvement of depression symptoms from the behavioral activation intervention. The mediation effect model and the path analysis statistical method will be used to investigate the mediating mechanism using the behavioral activation or inhibition motivation level as the treatment effect of the guided self-help behavioral activation intervention.

Ethics and Dissemination

Ethical Approval

This study has been reviewed and approved by the research ethics committee of the Mental Health Center of Chongqing. All participants will be asked to give verbal and written informed consent before inclusion and randomization. The study has been registered with the Chinese Clinical Trial Register (ChiCTR1900026066).

Informed Consent

All personal information collected during the study will be kept confidential and will be protected in accordance with the law. Participant names and identities will not be disclosed. The study data will be kept confidential and will be stored at the hospital. Only the medical staff, the ethics committee, and national health administration personnel involved in the study will have access to the confidential information for the necessary supervision and inspection.

Ethical and Safety Considerations

The study will obtain basic and psychological information through questions and questionnaires, with no risk of physical damage to the participants. To prevent the possibility that the assessment and intervention may cause the participants to be distressed, a well-trained clinical psychiatrist with over 10 years of professional experience will be prepared to intervene if participants report being distressed.

Results

As of July 2020, participant recruitment had not yet begun. Data collection is expected to be completed by December 2020. Data analysis is expected to be completed by June 2021. Results will then be disseminated to patients, to the public, to clinicians, and to researchers through publications in journals and presentations at conferences.

Discussion

This will be the first study in China to investigate guided self-help behavioral activation interventions for geriatric depression—a mental health condition which is currently underrepresented in research. The intervention is modular and adapted from manualized behavioral activation treatment for depression [23]. Patients who are older adults generally exhibit more avoidance behavior, which limits their participation in reinforcing activities (eg, leading to pleasurable or healthy outcome) [30].

The primary study will focus on the efficacy (including symptom reduction and remission rate) of the blended intervention (behavioral activation plus drug intervention) relative to that of the drug intervention. The conclusions of the study will be restricted to inpatients who are older adults with depression and who have no severe comorbid physical illness and organic brain diseases. Behavioral activation has great potential to relieve cognitive burden in patients, which may be most apparent in patients who are older adults with depression and with limited education. Furthermore, behavioral activation is easier to learn and to administer than other psychological interventions are and may therefore be more cost-effective for medical service providers. This study will provide data that will allow the effectiveness of behavioral activation to be evaluated in real-world participants with comorbid medical conditions and in community settings in future studies.

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Conflicts of Interest

None declared.

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Abbreviations

ICD-10: International Classification of Diseases, 10th edition

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Protocol

Impact of a Web-Based Clinical Decision Support System to Assist Practitioners in Addressing Physical Activity and/or Healthy Eating for Smoking Cessation Treatment: Protocol for a Hybrid Type I Randomized Controlled Trial

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Abstract

Background: Modifiable risk factors such as tobacco use, physical inactivity, and poor diet account for a significant proportion of the preventable deaths in Canada. These factors are also known to cluster together, thereby compounding the risks of morbidity and mortality. Given this association, smoking cessation programs appear to be well-suited for integration of health promotion activities for other modifiable risk factors. The Smoking Treatment for Ontario Patients (STOP) program is a province-wide smoking cessation program that currently encourages practitioners to deliver Screening, Brief Intervention, and Referral to treatment for patients who are experiencing depressive symptoms or consume excessive amounts of alcohol via a web-enabled clinical decision support system. However, there is no available clinical decision support system for physical inactivity and poor diet, which are among the leading modifiable risk factors for chronic diseases.

Objective: The aim of this study is to assess whether adding a computerized/web-enabled clinical decision support system for physical activity and diet to a smoking cessation program affects smoking cessation outcomes.

Methods: This study is designed as a hybrid type 1 effectiveness/implementation randomized controlled trial to evaluate a web-enabled clinical decision support system for supporting practitioners in addressing patients' physical activity and diet as part of smoking cessation treatment in a primary care setting. This design was chosen as it allows for simultaneous testing of the intervention, its delivery in target settings, and the potential for implementation in real-world situations. Intervention effectiveness will be measured using a two-arm randomized controlled trial. Health care practitioners will be unblinded to their patients'

treatment allocation; however, patients will be blinded to whether their practitioner receives the clinical decision support system for physical activity and/or fruit/vegetable consumption. The evaluation of implementation will be guided by the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework.

Results: Recruitment for the primary outcome of this study is ongoing and will be completed in November 2020. Results will be reported in March 2021.

Conclusions: The findings of the study will provide much needed insight into whether adding a computerized/web-enabled clinical decision support system for physical activity and diet to a smoking cessation program affects smoking cessation outcome. Furthermore, the implementation evaluation would provide insight into the feasibility of online-based interventions for physical activity and diet in a smoking cessation program. Addressing these risk factors simultaneously could have significant positive effects on chronic disease and cancer prevention.

Trial Registration: ClinicalTrials.gov NCT04223336; https://clinicaltrials.gov/ct2/show/NCT04223336

International Registered Report Identifier (IRRID): DERR1-10.2196/19157

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KEYWORDS

smoking cessation; physical activity; healthy eating; clinical decision support system; hybrid type 1

Introduction

Background

Modifiable risk factors such as tobacco use, physical inactivity, and poor nutrition account for a significant proportion of the preventable deaths in Canada [1]. These risk factors also frequently cluster together, thereby compounding the risks of morbidity and mortality [2-5]. Up to 93% of Canadians report consistently engaging in two or more unhealthy behaviors [6-8]. Among these risk factors, tobacco use continues to be the single most important modifiable risk factor for health care practitioners to intervene with their patients, as it is associated with the largest reductions in life expectancy and health-adjusted life expectancy [9,10]. Compared to nontobacco users, people who use tobacco are more likely to drink excessive amounts of alcohol, eat fewer fruits and vegetables, and report higher levels of physical inactivity [11,12]. The clustering of these modifiable risk behaviors not only puts individuals at an increased risk for cardiovascular disease and other chronic diseases such as cancer and diabetes but also can have significant impacts on the likelihood of successful smoking cessation [13-18]. In particular, physical activity has been shown to help support smoking cessation by reducing acute cravings and withdrawal symptoms [19-23]. The link between fruit/vegetable intake and smoking cessation is less clear; however, some studies have shown that postcessation weight gain (or the fear thereof) can be a significant barrier to quitting smoking [24-26].

Given this association, smoking cessation programs appear to be well-suited for integration of health-promotion activities for other modifiable risk factors. There are established evidence-based methods for identifying and addressing modifiable risk factors as part of a clinical appointment [27-30]. Specifically, the Screening, Brief Intervention, Referral to Treatment (SBIRT) method has empirical support and requires little time from health care practitioners to deliver (approximately 5-10 minutes) [31]. Moreover, brief interventions have been found to be effective in addressing different types of modifiable risk factors, including physical activity [32] and diet [33]. With respect to the type of behavioral intervention offered, evidence shows that risk communication and encouraging self-monitoring are more effective than other behavior change techniques (eg, provision of educational materials and facilitation) in promoting successful behavior change [34]. However, the impact of implementing SBIRT for other modifiable risk factors within a smoking cessation program is unknown. Since tobacco use is the most important modifiable risk factor for health care practitioners to address, it is important to ensure that interventions for these other risk factors do not reduce the likelihood of quitting smoking successfully.

The Smoking Treatment for Ontario Patients (STOP) program is a province-wide smoking cessation program that provides behavioral counseling and nicotine replacement therapy (NRT) at no cost to the participants. The STOP program has partnered with 153 (83%) family health teams, 61 (81%) community health centers, and 18 (75%) nurse practitioner-led clinics in Ontario. These primary care settings are not paid to offer the program but are provided with no-cost NRT to dispense to participants as needed. Treatment is tailored by the health care practitioner and patients are eligible for up to 26 weeks of NRT during their time in the program (12 months). Health care practitioners will typically meet with participants every 2-4 weeks to assess their progress and up to 4 weeks of NRT is dispensed in any given visit. The behavioral counseling provided by the health care practitioners is primarily guided by the principles of motivational interviewing [35]. In addition, STOP health care practitioners are encouraged to deliver SBIRT to patients who are experiencing depressive symptoms [36] or consuming excessive amounts of alcohol [37] via a web-enabled clinical decision support system (CDSS). However, there is no built-in CDSS for physical inactivity and poor diet.

A CDSS is a computer app designed to present patient-specific, actionable information to help support practitioners in determining diagnoses and treatment approaches [38,39]. Given the increased use of electronic medical records in primary care offices, broader implementation of CDSSs has become possible, offering an opportunity to improve evidence-based care.

Objectives

The aims of this study are to: (1) assess whether adding a CDSS for physical activity and diet to a smoking cessation program affects smoking cessation outcomes, and (2) quantitatively and qualitatively assess the implementation of the study using the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework.

Methods

Trial Design

The study will utilize an effectiveness/implementation hybrid type 1 design for the evaluation [40]. This design was chosen as it allows for simultaneous testing of the intervention, its delivery in target settings, and the potential for implementation in real-world situations; using a setting in which there is already clinical momentum reduces risks with potentially high benefit [40]. This trial will be made operational via the STOP program. Intervention effectiveness will be measured using a two-arm randomized controlled trial. Health care practitioners seeing patients randomized to the intervention arm (Group A) will receive computer alerts when a patient does not meet the national guidelines of nutrition or physical activity. They will then be guided to deliver a brief intervention to the patient. Health care practitioners seeing patients randomized to the treatment-as-usual arm (Group B) will not receive computer alerts for physical activity and fruit/vegetable consumption. The evaluation of implementation will be guided by the RE-AIM framework [41].

Preimplementation

The implementation of this project will be guided by the Interactive Systems Framework (ISF) for dissemination and implementation. The ISF suggests that there are three interacting systems involved in translating research findings to practice: synthesis and translation systems, support systems, and delivery systems [42]. In this study, the delivery systems will be the health care practitioners in primary care clinics, and people who smoke and who do not meet the national guidelines of diet or physical activity will be the recipients of the intervention.

At the time of submission of this manuscript, we had already conducted two community-informed engagement events with the target population (STOP program participants) to cocreate risk communication messages that health care practitioners could use with their patients and a self-monitoring resource for patients to track their risk behaviors. These resources are based on best practices and patient experiences, and form part of the ISF synthesis and translation systems [42]. As part of the support system, we developed and delivered an interactive webinar training for health care practitioners that combined the latest evidence on behavior change approaches and the findings from the engagement events with STOP participants. The webinar provides concrete advice as to why and how health care practitioners should address physical activity and fruit/vegetable consumption, and how these aspects can be incorporated in a smoking cessation treatment program. In the past, STOP health care practitioners have expressed reservations toward addressing multiple behaviors; therefore, this webinar also trains health care practitioners on how to address 2-3 behaviors simultaneously to produce maximum change in participants [43].

Participants

Participants will be treatment-seeking smokers that enroll in the STOP program. Individuals interested in enrolling in the program either self-refer or are referred by their health care practitioner. Clinics enroll their patients into the STOP program using the STOP portal, an online portal that allows for data collection and management. The current portal already has a CDSS [44,45] to guide health care practitioners with the delivery of a brief intervention for patients who also have current or past depression, as defined by the Patient Health Questionnaire (PHQ-9) [46], or consume excessive amounts of alcohol, as defined by the Alcohol Use Disorders Identification Test (AUDIT-C and AUDIT-10) [47].

At the time of enrollment, all patients are asked to provide informed consent prior to seeing their health care practitioner. Using the online portal, the health care practitioner completes the baseline enrollment survey with the patient. This survey has screening questions for tobacco use and related measures, including alcohol use [47], depression [46], physical activity [48], and fruit/vegetable consumption [49].

The implementers of this CDSS pathway will include health care practitioners from a wide variety of disciplines (eg, nurses, pharmacists, social workers) who have been trained by the STOP team. They also belong to the STOP program's Community of Practice where they engage in continuous learning through informal (eg, listserv) and formal (eg, mentoring phone calls, webinars) mechanisms.

Setting and Location

The trial will take place in family health teams (n=153), community health centers (n=61), and nurse practitioner–led clinics (n=18) in Ontario, Canada implementing the STOP program and using STOP's online portal as of November 29, 2019.

Inclusion Criteria

When a patient is enrolling in the STOP program, the STOP enrollment survey must be delivered by the health care practitioner using the online STOP portal. At the time of enrolling in the STOP program, patients must also be below the national guidelines for physical activity [48] or fruit/vegetable consumption [49]. A low level of physical activity is defined as engaging in less than 150 minutes of moderate/vigorous exercise per week [48]. A low level of fruit/vegetable consumption is defined as consuming less than 7 servings (women) or 8 servings (men) of fruit/vegetables daily in accordance with the 2007 Canadian Food Guide [49].

Patients must also provide at least one piece of contact information (phone number or email address) to allow for follow up to be conducted at 6 months.

Randomization

Patients will be randomly allocated at the time of enrollment to the intervention arm (Group A) or control arm (Group B) at a

1:1 allocation ratio. The random allocation sequence is generated automatically and internally by the STOP portal. The study team, health care practitioners, and participants do not have access to this automatically generated randomization. Health practitioners treating participants randomized to Group A will have a CDSS for physical activity and fruit/vegetable consumption available to them, whereas participants randomized to Group B will receive treatment as usual in the STOP program.

Blinding

Health care practitioners will not be blinded to the patient's treatment allocation, and they will see both intervention and control patients. Patients will be blinded to whether their health care practitioner receives the CDSS for physical activity and/or fruit/vegetable consumption.

Intervention

As described above, the STOP portal currently has a CDSS that screens patients and alerts health care practitioners when their patients report risky alcohol use [44] or depressive symptoms [45]. Health care practitioners are then prompted to address these risk factors as part of the patient's smoking cessation treatment. Both Group A (intervention) and Group B (control) will continue to have the CDSS for alcohol use and depressive symptoms.

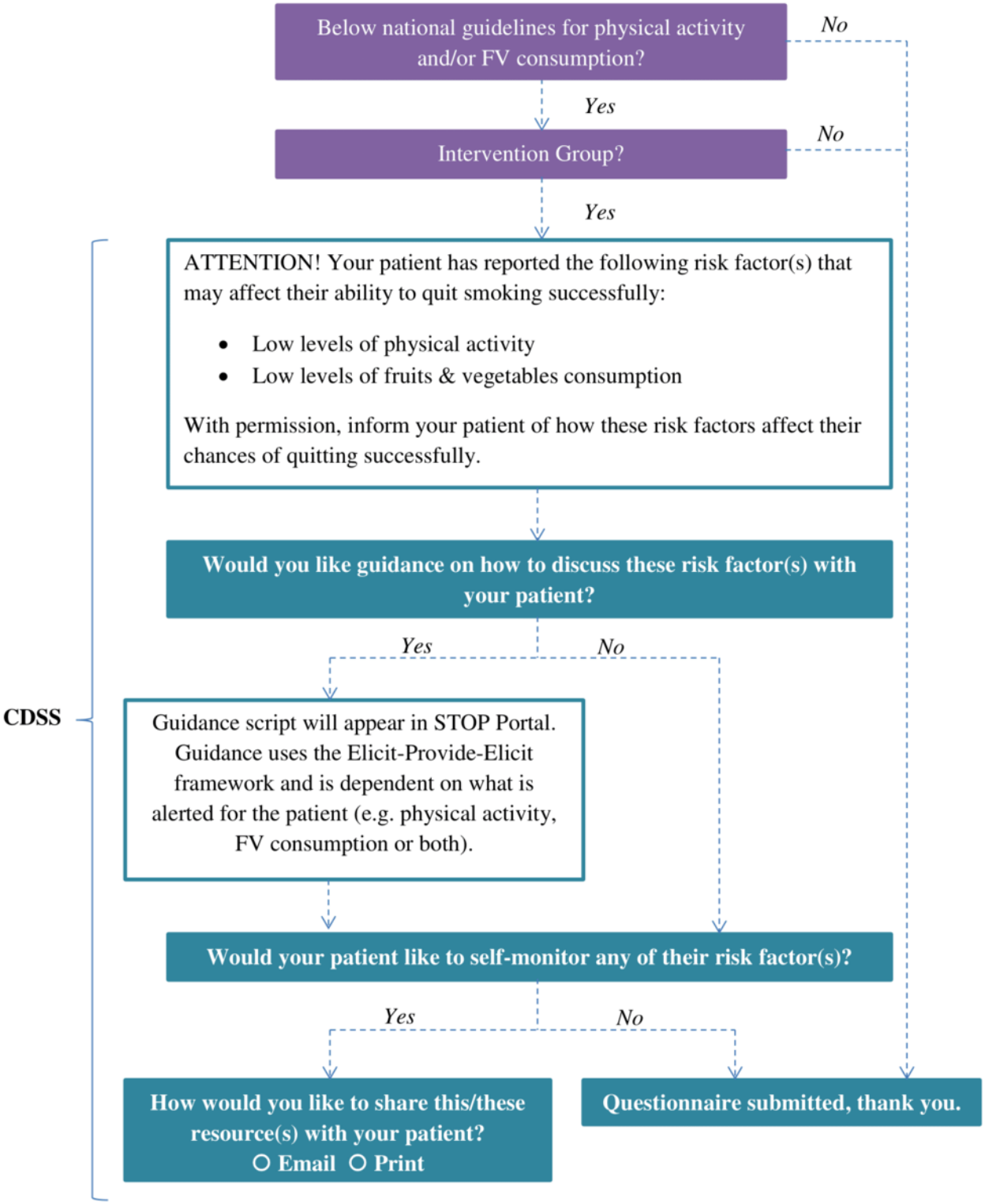
Intervention (Group A)

The STOP portal will be adapted to provide a CDSS for physical activity and/or fruit/vegetable consumption (Figure 1). At the time of enrollment, the CDSS will: (1) screen patients for their physical activity and fruit/vegetable consumption levels, (2) provide health care practitioners with an alert when the patient is not meeting guidelines for physical activity and fruit/vegetable consumption, and (3) guide health care practitioners to intervene with the patient using the following steps.

Step 1 involves risk communication with their patient to raise awareness of the identified risk factors. This includes sharing the information in the alert, which lists the specific risk factors (eg, low levels of physical activity) for the patient, and discussing how each risk factor affects their patient's health and smoking cessation treatment. The CDSS also includes optional guidance for health care practitioners on how to provide risk communication using the Elicit-Provide-Elicit framework [50]. The guidance message will remind health care practitioners to use positively framed risk communication messages. This was based on the results of the engagement events with STOP participants.

In step 2, a customized self-monitoring resource for the risk factors is provided to patients who want to self-monitor as a part of their smoking cessation treatment. The self-monitoring resource (see Multimedia Appendix 1), which health care practitioners will be able to print or email to their patients, is a 1-page weekly tracking sheet, including the following key features: ability to track multiple behaviors simultaneously on the same page; ability to record the number of cigarettes smoked, in addition to the other behaviors they chose to monitor; and setting weekly goals.

Figure 1. Study workflow diagram. FV: fruits and vegetables.



Control (Group B)

Health care practitioners of patients randomized to Group B will experience the STOP portal as usual. STOP participants will also be asked screening questions for physical activity and diet; however, health care practitioners are not provided with an alert about their physical activity and fruit/vegetable consumption levels, and are not prompted to take any actions to address these two behaviors. Practitioners treating patients in Group B are only provided with the CDSS for depressive symptoms and alcohol use, which has been available in the STOP portal prior to this trial.

Outcomes

The primary outcome of the study is self-reported smoking cessation at 6-month follow up. This dichotomous outcome will be measured by a negative response to the 7-day point prevalence abstinence question: “Have you smoked a cigarette, even a puff, in the last 7 days.” Researchers have shown that

self-reporting for smoking status is highly consistent with biochemical assessments of smoking [51-54].

The secondary outcomes of the study will be a self-reported change in physical activity levels and fruit/vegetable consumption levels from baseline to 6-month follow up. Changes in physical activity will be assessed using an adapted Exercise Vital Signs screener [55] that consists of two questions: "On average, how many days per week do you engage in moderate-to-strenuous (vigorous) exercise (like a brisk walk)?" and "On these days, for how many minutes do you typically exercise at this level?" This screener has been validated against step counts [55]. Changes in fruit and vegetable consumption will be measured using a single question: "In a typical day, how many total servings of fruits and vegetables do you eat? (1 serving is 1/2 cup of fresh, frozen, or canned fruits or vegetables, or 1/2 cup of 100% juice. Please DO NOT include potatoes)."

These questions will be administered at the time of enrollment in the STOP program and at the 6-month follow up. Responses to the self-report questions for both the primary and secondary outcomes will be collected via phone or email. We will use the RE-AIM framework to organize our implementation evaluation, which is summarized in Textbox 1.

Textbox 1. RE-AIM framework for implementation and evaluation of the trial.

- REACH:

  Has the reach of the STOP portal changed? (The reach will be defined as the number of STOP enrollments completed online).
- EFFECTIVENESS:

  What proportion of participants from the intervention vs control groups report smoking cessation at 6-month follow up? (please see Outcomes section for details)
- ADOPTION:

  What proportion of intervention group participants received risk communication and at least one self-monitoring resource?
- IMPLEMENTATION:
  - What proportion of participants in Group A accepted the self-monitoring resource for physical activity and/or fruits/vegetables consumption?
  - What are the barriers and facilitators health care practitioners report to delivering the intervention as intended?
  - What are some barriers and facilitators faced by participants in receiving the intervention?
- MAINTENANCE:

  What proportion of intervention participants who were quit at 6 months were also quit at the 12-month follow up?

Sample Size

A sample size of 3998 (1999 per group) is needed to detect a clinically meaningful difference in smoking cessation outcome between groups at 6 months. Using past STOP data, and after accounting for nonresponse, we estimate the proportion of patients who will quit smoking at 6 months to be 0.26, and set α to .05 and the power to 80%. For the effect size, we use an absolute difference in proportions of 0.04, which is an established standard for clinical significance in smoking cessation [56].

Based on past experience in conducting trials using the STOP platform, we anticipate a loss to follow up of 20%. This increases the necessary total baseline sample to 4998 (2499 per group). Based on enrollment in 2017-2018, we estimate that the required sample size for the primary outcome will be achieved in approximately 7 months. However, as the recruitment and follow-up periods are likely to overlap slightly, we will monitor the follow-up rate being achieved. If this rate is lower than anticipated, we will consider extending recruitment to achieve an adequately powered analysis sample.

Statistical Analysis

Analysis of the primary and secondary outcomes will be performed using the intention-to-treat principle. Patients will be analyzed in the study arm to which they are assigned (control vs intervention group). Descriptive statistics (without testing) will be used to summarize patient-level baseline characteristics in the intervention and control groups.

We will test for a group difference in our primary outcome using a chi-square test. For our secondary outcomes, we will test for group differences in change over time by regressing the 6-month outcomes on the baseline measures and group. We will use linear regression for total exercise time and ordinal logistic regression for total fruit and vegetable consumption.

Although the STOP program comprises many separate clinical sites, analyses using mixed-effects models indicate that any true site effects are quite small. We therefore do not anticipate a need to account explicitly for clustering. However, we will test this by measuring the site-level intraclass correlation, and will analyze our data using random intercept models if deemed to be appropriate.

To understand wider associations between our outcomes and participant characteristics, we will also perform multivariate analyses, including logistic regression for smoking cessation, linear regression for exercise, and ordinal logistic regression for fruit and vegetable consumption. In these models, we will include education, income, substance use, mental health diagnoses, gender, age, and the Heaviness of Smoking Index [57] as independent variables.

Primary and secondary outcomes will only be available from patients who complete a 6-month follow-up survey. As a result, we anticipate that approximately 20% of these will be missing, and that there will also be some missing values in baseline variables. We will address these missing data using multiple imputation with chained equations. Our missing data model will include all 3 outcomes, the variables from our secondary (adjusted) analyses, and auxiliary variables, including smoking status from STOP follow-up assessments performed at 3 and 12 months after baseline (where available), smoking status at the last clinical visit, number of visits, clinical counseling received, and type and duration of NRT prescribed. A statistical analysis plan will specify the number of imputed datasets to be created, the models to be used, and the variables to be incorporated.

Data Security and Quality Assurance

Data will be stored in secure computerized files and the informed consent forms will be kept in locked cabinets in the study team's locked offices. The STOP portal uses two different database encryption mechanisms (transparent database encryption and cell-level encryption) to protect the online data from intrusion. The study team will conduct monthly review of the data on the STOP portal to ensure the CDSS continues to operate correctly throughout the study.

Ethical Approval and Trial Status

This study was reviewed by the Research Ethics Board at the Centre for Addiction and Mental Health, Toronto, Ontario, Canada (119-2018). This trial is registered with ClinicalTrials.gov (NCT04223336).

Results

As of April 2020, interactive webinar training was delivered to STOP health care practitioners, and recruitment has started but is not yet complete. We estimate that recruitment will be completed in November 2020. Results will be reported in March 2021.

Discussion

This clinical trial provides a novel method for addressing physical activity and fruit/vegetable consumption as part of a smoking cessation program. Smoking cessation programs continue to be essential public health initiatives. The literature shows that with every two individuals who quit smoking, at least one life is saved from a tobacco-related death [56]. Furthermore, in Ontario, physical inactivity and inadequate diet contribute to approximately 40% of all deaths [10]. If these risk factors can be addressed simultaneously, it could have significant positive effects on public health.

Moreover, delivery of this intervention via a web-based portal allows for rapid, system-wide implementation. The STOP program enrolls over 23,000 participants per year and the impact of this intervention could be widespread. The findings from this study can help inform future development and integration of interventions for other modifiable risk factors within smoking cessation programs.

We chose to conduct a hybrid type I design since our primary aim is to test the effects of a clinical intervention (adding a CDSS for physical activity and fruit/vegetable consumption) on relevant outcomes (smoking cessation at 6 months, and change in physical activity levels and fruit/vegetable consumption levels from baseline to 6 months). However, we also want to gather information on implementation outcomes from the study, including whether it changes the reach of the program, the adoption of the intervention (whether health care practitioners follow the recommendations of the CDSS and patients accept the resource), and potential barriers and facilitators to real-world implementation of the intervention. This design will provide high reward as the implementation research offers additional context that will help with understanding whether a clinical trial is effective or ineffective.

We chose to evaluate effectiveness via a randomized controlled trial with randomization at the individual level, as this is feasible (in both arms, the health care practitioner can respond directly based on the CDSS) and provides more power compared to cluster randomized controlled trials for detecting any clinically significant changes in the outcomes of interest [58].

There are a few potential study limitations that need to be acknowledged. Health care practitioners will not be blinded to the patient's treatment allocation and will be seeing both intervention and control patients. The lack of blinding can lead to possible group contamination as health care practitioners may apply their knowledge from the intervention to the control group. The potential learning effect may decrease the effect of the trial. However, the self-monitoring resource for physical activity and diet are only accessible to intervention patients, which will help to reduce the cross-contamination. Randomization at the organizational level would not completely eliminate the risk of contamination as some health care practitioners work at multiple organizations.

The results of this trial will be disseminated through peer-reviewed publications and conference presentations. Results will also be presented and communicated appropriately to STOP health care practitioners and the funders for this initiative.

The findings of the study will provide much needed insight into whether other modifiable risk factors can be addressed simultaneously as a part of a smoking cessation program without affecting the individual's ability and success in quitting smoking. If the results of the study are positive (ie, more intervention group individuals quit smoking) or show no negative effect on smoking cessation, we can continue to offer physical activity and diet interventions as part of smoking cessation programs. Our evaluation of the implementation of the study will also provide insights into whether CDSS interventions are an appropriate method for promoting physical activity and diet interventions as part of smoking cessation treatment.

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Authors' Contributions

All authors have contributed to the design, execution, and writing of this protocol, and have approved the submitted version.

Conflicts of Interest

The authors declare that they have no conflicts of interests with respect to this manuscript; however, some authors have general disclosures to report. PS reports receiving grants and/or salary from Centre for Addiction and Mental Health, Ontario Ministry of Health and Long-Term Care, CIHR, Canadian Centre on Substance Use and Addiction, Public Health Agency of Canada, Medical Psychiatry Alliance, Canadian Cancer Society Research Institute, Cancer Care Ontario, and the Ontario Institute for Cancer Research. PS also reports receiving funding from the following commercial organizations: Pfizer Inc/Pfizer Canada, Bhasin Consulting Fund, Shoppers Drug Mart, and Patient-Centered Outcomes Research Institute. PS has received consulting fees from Pfizer Inc/Pfizer Canada, Johnson & Johnson Group of Companies, and MedPlan Communications. Through an open tender process, Johnson & Johnson, Novartis, and Pfizer Inc are vendors of record for providing smoking cessation pharmacotherapy, free or discounted, for research studies in which PS is the principal investigator or coinvestigator. MH reports receiving consulting fees from Alkermes. WD reports grant funding from Pfizer Inc, Abbott Laboratories, and Medical Psychiatry Alliance. WD also reports stock ownership in Abbott Laboratories.

Multimedia Appendix 1
Self-monitoring resource.
[PDF File (Adobe PDF File), 269 KB - resprot_v9i9e19157_app1.pdf]

Multimedia Appendix 2
CONSORT E-HEALTH checklist (v 1.6.1).
[PDF File (Adobe PDF File), 1536 KB - resprot_v9i9e19157_app2.pdf]

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Abbreviations

AUDIT: Alcohol Use Disorders Identification Test
CDSS: Clinical Decision Support System
ISF: Interactive Systems Framework
NRT: nicotine replacement therapy
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
SBIRT: Screening, Brief Intervention, Referral to Treatment
STOP: Smoking Treatment for Ontario Patients

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Protocol

Comparative Effectiveness of Two Nonsurgical Treatments to Reduce Oral Health Disparities From Untreated Tooth Decay in Older Adults: Protocol for a Cluster Randomized Trial

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Abstract

Background: The majority of dental caries lesions in older adults are at the gumline, at the edges of failed fillings and crowns, and in the surfaces of roots after gum recession. These lesions are difficult to restore with conventional surgical treatments using a dental drill and restorations often fail. Clinical guidelines are general and apply treatments that were designed for younger individuals in the dental care of older adults.

Objective: This study will compare the effectiveness of 2 evidence-based nonsurgical strategies to manage dental caries lesions in adults aged 62 or older: (1) biannual topical application of silver diamine fluoride versus (2) atraumatic restorative treatment + biannual fluoride varnish.

Methods: A cluster randomized clinical trial is being conducted in 22 publicly subsidized and other low-income housing facilities/sites (Arm 1: 11 sites, 275 participants; Arm 2: 11 sites, 275 participants). At baseline, participants will be screened for caries lesions. Those with nonurgent lesions will be treated according to the treatment arm to which the housing site was randomly assigned. The primary outcomes are caries lesion arrest, tooth sensitivity, and tooth pain at 52 weeks after treatment. Analytic methods for the primary aim include a generalized estimating equation approach to determine noninferiority of silver diamine fluoride relative to atraumatic restorative treatment + fluoride varnish treatment.

Results: The trial was funded in April 2019. Enrollment began in September 2019 and results are expected in June 2023.

Conclusions: This study will inform the standard of care for treating caries lesions in older adults. If effective, either of these interventions has broad applicability in clinical and community-based settings.

Trial Registration: ClinicalTrials.gov NCT03916926; https://clinicaltrials.gov/ct2/show/NCT03916926

International Registered Report Identifier (IRRID): DERR1-10.2196/17840

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KEYWORDS

dental caries; older adults; atraumatic restorative treatment; silver diamine fluoride; fluoride varnish

Introduction

Over 96% of US adults aged 65 or older have had at least one caries lesion (cavities or tooth decay) in the permanent teeth [1]. About 37% of adults aged 65 or older have tooth decay in exposed root surfaces [1]. Dental caries is the primary cause of tooth loss in older adults. Further, untreated tooth decay is disproportionately found in minority and low-income older adults [2]. Consequently, tooth loss is also significantly higher in non-Hispanic Blacks compared with other groups [2], who may also have vulnerable root surfaces because of untreated periodontal diseases [3].

The progression of oral diseases adversely affects general health [3] and individuals with tooth loss reported poorer oral

health-related quality of life [4]. A 2018 oral health screening and survey of older adults highlighted that many, especially those with low incomes, are living with significant untreated dental disease with impacts on chewing, nutrition, and overall well-being that requires immediate attention and focus [5].

A recent study of 202 older adults from 16 publicly subsidized housing units in Northeast Ohio found that the proportion with untreated caries lesions (58%) is twice the national average (28%) [6]. These 202 older adults reported the following symptoms: 40% with tooth pain, 54% with tooth sensitivity, 23% with bleeding gums, 35% with loose teeth, and 67% with dry mouth [7]. All had 1 medical condition and 83% had 2 or more medical conditions [7]. Nationally, 92% of US older adults are reported to have at least one medical condition, and 77% have 2 or more conditions [8]. Poor oral health contributes to worsening general health in older adults [9-15].

Conventional restoration of cavities in older adults is more complex than in younger individuals because of age-related changes to the enamel, dentin, and pulp chamber [16]. The majority of such cavities occurs at the gumline, at the periphery of failed fillings and crowns, and in root surfaces after gum recession [17]. These cavities are difficult to restore with conventional surgical treatments using a dental drill and the restored lesions often fail [18]. A randomized trial in older adults with root caries lesions found similar restoration survival rate (87% vs 91%) with atraumatic restorative treatment (ART; using high-viscosity glass ionomer cements [GICs]) versus conventional fillings, respectively [19]. Professional applications of sodium fluoride varnish (FV), thymol chlorhexidine varnish, and silver diamine fluoride (SDF) are also effective in preventing new lesions or arresting existing ones [20]. Annual professional applications of topical 38% SDF were effective in arresting and preventing root caries lesions among older adults in clinical trials [21-23]. A systematic review and meta-analysis support the use of SDF [24,25], the use of ART with high-viscosity GICs [26], and the use of 5% FV [27] for caries management in older adults. However, there have been no trials of comparative effectiveness of nonsurgical caries intervention strategies

Therefore, the objective of this randomized clinical trial is to compare 2 nonsurgical evidence-based strategies for untreated tooth decay: SDF versus ART + FV to improve clinical (caries lesion arrest) and patient-reported (tooth pain, sensitivity) outcomes among community-dwelling older adults. Both intervention arms can be delivered by dental hygienists in alternative (nondental clinic) settings. *Nonsurgical* in this context means treatments that do not require the use of a dental drill. The reason this is a disparity issue is that the field of dentistry lacks specific standards of care for older adults, especially those who have low income, with multiple medical problems, physical frailty, and dementia. Instead, the typical dentist tries to apply surgical treatments developed for younger, healthier individuals, with predictably poor results.

Methods

Trial Design

This is a multisite, single-blind, parallel-arm, community-based cluster randomized controlled trial with 2 arms. The trial has been registered with Clinicaltrials.gov (NCT03916926) and is currently in the recruitment phase. This protocol report follows the SPIRIT [28] and CONSORT (Consolidated Standards of Reporting Trials) guidance [29].

Research Objectives and Hypothesis

The primary aim is to compare 2 evidence-based strategies in low-income older adults aged 62 or older followed for 52 weeks (1 year): a “simple medical” strategy of topical application of SDF (Arm 1) versus a “typical dental” strategy consisting of ART and topical application of FV (Arm 2). The rationale for adding FV to the ART arm is that ART has a direct effect on the treated tooth and perhaps on the adjoining tooth surface while FV has whole mouth benefits, as does SDF. Our primary hypothesis is that simple medical treatment (Arm 1) is not inferior to typical dental treatment (Arm 2) for clinical (caries lesion arrest) and patient-reported (tooth pain/hypersensitivity) outcomes at 52 weeks after treatment. Our secondary hypothesis is that the simple medical treatment (Arm 1) is not inferior to typical dental treatment (Arm 2) for clinical (new caries lesions) and patient-reported (oral health quality of life) outcomes at 52 weeks after treatment.

Participant Recruitment, Enrollment, and Retention

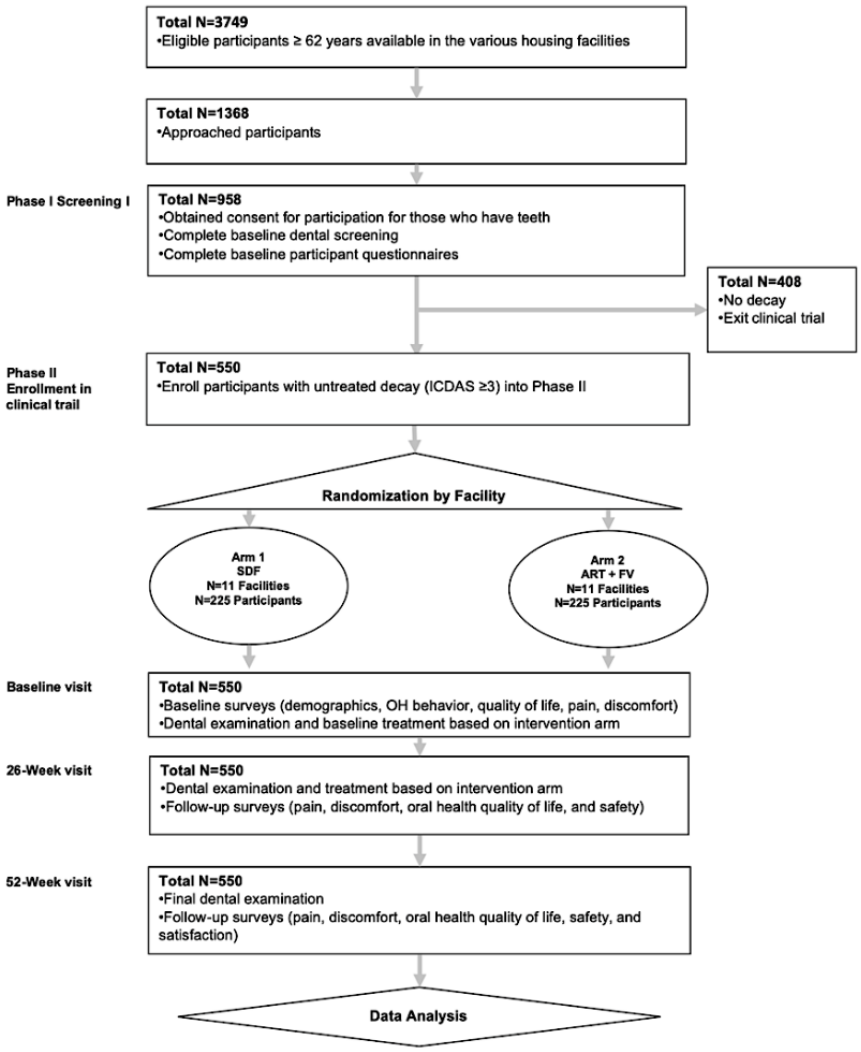
Study sites are 22 housing facilities for adults of low income in Northeast Ohio. In these facilities, residents live independently in individual apartments. Older adult tenants aged 62 or older will be approached for participation. Those who self-report that they are without teeth will not be recruited. The recruitment will follow a 2-stage process: (1) all participants consented will participate in the dental screening; (2) participants found to have nonurgent cavities (ie, those without irreversible pulpitis, periapical abscess or cellulitis or facial swelling) at the screening and who fulfill the inclusion criteria (see below) will be enrolled into the clinical trial.

Service coordinators at the facilities will serve as site liaisons. The study principal investigator/project manager will provide the coordinators with an introductory letter/flyer (Multimedia Appendix 1) containing study information and ask that it be given to tenants and posted in public areas. The coordinators will arrange an informational meeting (study dentist will give a talk on the interventions as suggested by our stakeholders), and study staff will present information regarding participation at scheduled group events such as tenant meetings or health fairs. For planning purposes, coordinators will have a sign-up sheet for those interested in the sessions. Study staff will schedule potential participants for one-on-one sessions at the housing facility to obtain informed consent and collect a baseline survey. A dental examination and treatment appointments will then be scheduled at each facility according to a designated roll-out schedule for each facility, approximately 1-2 weeks following consent and baseline data collection.

According to the 2-stage process for enrollment, the *initialinclusion criteria* of participants are as follows: provide signed and dated consent form, willing to comply with all study procedures, being available for the duration of the study (1 year), male or female, aged 62 or older, and living in a participating facility. In the second stage of enrollment, *additional inclusion criteria* for continuation and participation in the randomized controlled trial are based on the dental screening. A participant must have at least one untreated root surface or coronal caries lesion on any permanent tooth with an International Caries Detection and Assessment System (ICDAS) II [30] active lesion score of 3 or greater (localized enamel cavity to extensive cavity). At this stage, further *exclusion criteria* are sensitivity to silver or other heavy-metal ions or oral ulcerative gingivitis or stomatitis, which prevents the potential participant from receiving study treatment. The study has a 26-month recruitment time frame that started in October 2019.

Participants are followed at 26 weeks (6 months) and 52 weeks (12 months) that includes dental examinations/treatment and survey completion. This follow-up period is consistent with another caries arrest trial [21]. The schematic of the study design is presented in Figure 1.

Figure 1. Study design.



All visits will occur at the housing facility where the individual participant resides. Several strategies will be used to retain the participants: promotional items (ie, pens, magnets) with the study logo and contact phone number at recruitment (alternate contact information for family/friends that may allow to reach the participant if primary contact information becomes invalid will be obtained at recruitment); annual birthday/holiday cards will be sent to participants to maintain contact; and newsletters will be sent twice a year with updates on the study's progress including reminders to update their contact information (by phone or postal mail). Assistance from service coordinators or other facility staff will be sought to maintain contact with hard-to-reach/contact participants. Cash incentives will be given to the participants at the baseline screening and examination (US $25); those enrolled in the clinical trial will receive additional incentives at 26-week follow-up visit (US $40), and at the 52-week visit (US $40) for the completion of all study procedures.

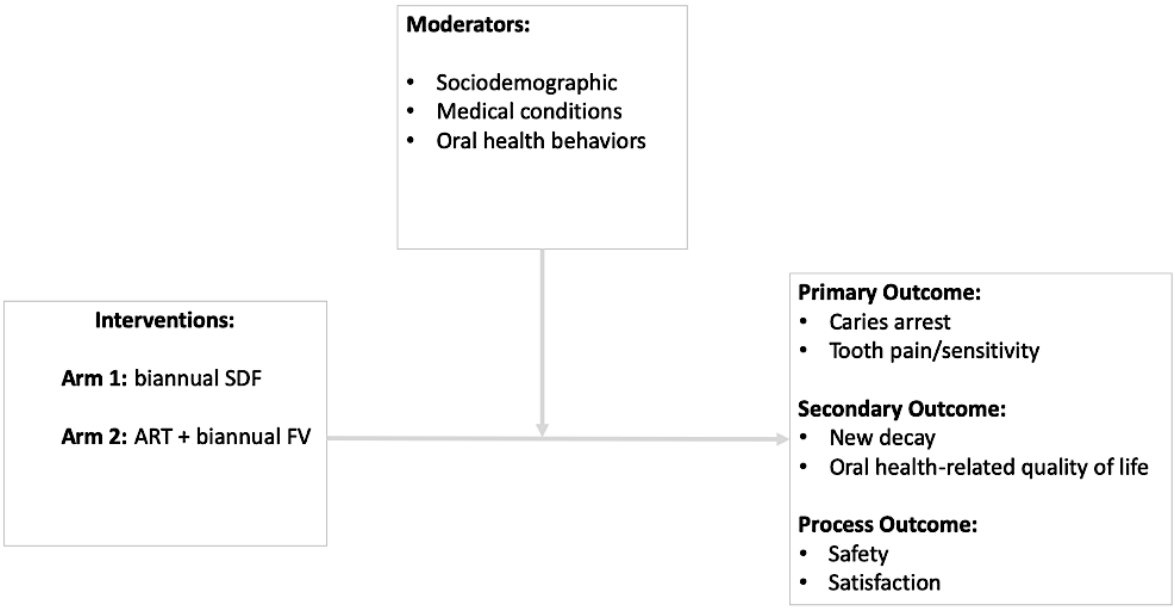
The Case Western Reserve University Institutional Review Board approved all study procedures (STUDY20190481) and written informed consent is obtained from the participant.

Interventions

Conceptual Model and Design

Figure 2 shows the study model for the intervention. The comparative effectiveness of "simple medical" (ie, SDF) versus "typical dental" (ie, ART + FV) intervention in this study is focused on the person level to address the unique oral health needs of low-income older adults. Figure 2 indicates that the proposed intervention is hypothesized to arrest caries in older adults with untreated caries and prevent tooth pain/hypersensitivity (primary outcomes), and prevent new decay and improve oral health-related quality of life (secondary outcomes) over a 52-week follow-up period. Safety and satisfaction measures are process outcomes that are critical to assess for sustainability and dissemination of the interventions. Factors likely to moderate the effectiveness of interventions are sociodemographics, chronic medical conditions, and oral health behavior. These baseline (pretreatment) variables are also considered as prognostic variables (related to outcomes).

Figure 2. Conceptual Model.



Specifics of the Intervention

Arm 1

The treatment will be biannual application (at baseline and 26 weeks) of topical 38% SDF (Advantage Arrest; Elevate Oral Care, LLC) following manufacturer's instructions and published guidelines [31].

Arm 2

The treatment will be ART [19] with the cavity restored at baseline with resin-reinforced GIC (GC Fuji Automix LC; GC America Inc). Participants in this arm will also receive biannual (at baseline and 26 weeks) topical FV application (FluoriMax 2.5% NaF Varnish; Elevate Oral Care, LLC) applied according to manufacturer's instructions.

Administration of Intervention

The treatments are administered by licensed dental hygienists supervised by a study dentist. All nonurgent cavitated lesions will be considered for treatment in both arms. For application of ART, if there are too many teeth to be treated, then priority will be in this order: (1) anterior teeth; (2) any tooth retaining an appliance (eg, partial denture); (3) teeth that are in occlusion such as biting teeth. The procedures are presented in the following sections

Arm 1

SDF will be applied to all carious lesions at the baseline visit and the 26-week visit. The cavity will be cleaned with a tooth brush to remove debris, isolated with cotton rolls, and then SDF from a single-use ampule will be applied using the manufacturer-supplied brush. The lesion will be allowed to air dry for about 1 minute. The participants can then resume normal activity with no restriction.

Arm 2

ART will be administered only at the baseline visit, but FV will be applied biannually at the baseline and the 26-week visit. First, the cavity will be isolated with cotton rolls. The dental hygienist will remove debris with moistened cotton pellets. Then, soft demineralized tooth structure will be removed with a spoon excavator at the periphery of the lesion by the supervising dentist, where the shape of the cavity permits access with the spoon excavator. A manual tooth brush and plain pumice will be used to remove any further loose material. The cavity will be washed with water. Second, the lesion will be conditioned with the manufacturer-supplied polyacrylic acid for 10-15 seconds, rinsed with water, and then resin-reinforced glass ionomer restorative will be inserted into the cavity using the manufacturer's delivery device and coated with a protective gel. The restoration will then be polymerized for 20 seconds using a manufacturer-supplied visible light. Finally, FV will be applied to all tooth surfaces using the manufacturer's brush

system. The material will be allowed to dry for 3-5 seconds. The patient will be instructed to avoid eating or dental hygiene for 4 hours.

Procedures for Training Interventionists and Monitoring Intervention Fidelity

The study interventionists (dental hygienists) will receive didactic and clinical instruction in the application of SDF, ART, and FV from 2 gold-standard experts who have been recognized as national academic and clinical leaders in the application of these interventions. The hygienists will undergo a 2-day training and calibration exercise with extracted teeth and applying the intervention on patients. To be certified, the study hygienist must demonstrate mastery: by completing at least three ART procedures on older adult patients with cavities and at least one SDF and FV treatment on an older adult patient; and also complete a written examination on procedures.

To ensure study treatment is delivered per protocol and meets the requirements of Ohio law, a study dentist will be present for supervision. If there is a problem with the delivery of the treatment or adherence to protocol, then the hygienists will be given corrective training. In addition to direct supervision, a research staff will take random images of ART restorations. A digital camera (Canon EOS Rebel T2i 550D, Canon Inc.) fitted with a 100-mm macro-lens and a ring flash will be used. The research staff have been trained in using the camera. The research staff randomly selects from among the participants receiving ART treatment on any particular day. These clinical photographs will be reviewed on a quarterly basis by the supervising dentist and corrective training will be provided to the hygienists if there is a problem.

Another third gold-standard expert (with expertise nationally and internationally) will calibrate/train the examiners in the ICDAS protocol in a separate 4-day training session. This will include a didactic presentation and clinical examination of a few older adult patients with the instructor. The calibration session consists of the gold standard expert and the hygienist examining 10-15 older adult patients separately to calculate interrater reliability. The hygienist and dentists completed these training sessions in August 2019 prior to participant recruitment.

Dental examinations will be conducted in a portable dental chair in the housing facility. A total of 4 examiners have been trained. The interexaminer reliability was good to excellent for ICDAS lesion severity ($w\kappa$=0.62-0.68), lesion activity ($w\kappa$=0.62-1.0), and fillings ($w\kappa$=0.78-0.86), respectively. Examiners will not utilize dental radiographs. Examiners will be recalibrated before follow-up. At follow-up, the examiner will also not have access to the results of the first examination to avoid detection bias. A study dentist is present at each housing facility to supervise the examinations and treatment.

Data Collection

Participants' schedule for data collection is given in Table 1. A summary of the data collected is as follows.

Table 1. Summary of study measures and timeline in the older adults trial.

Variable type, measure, and scale	Source	Timeline
Intervention by study arms		T_0[a], T_{26}[b]
Arm 1: Biannual SDF[c]		
Arm 2: ART[d] + biannual FV[e]		
Primary outcome		
Clinical dental examination		T_0, T_{26}, T_{52}[f]
Caries arrest, frequency of treated surface/teeth that are arrested (%)	ICDAS[g] coronal and root [30]	
Self-reported evaluation		T_0, T_{26}, T_{52}
Tooth pain/sensitivity, overall score	PROMIS version 1.0 – Pain Intensity 3a (Modified for dental) [32] and Dental Discomfort Questionnaire (Modified for adults from [33])	
Secondary outcomes		
Clinical dental examination		T_0, T_{26}, T_{52}
New decay, frequency of new decayed surface/teeth (%)	ICDAS coronal and root [30]	
Self-reported evaluation		T_0, T_{26}, T_{52}
Oral health quality of life, GOHRQoL[h] overall score	GOHRQoL [34]	
Process outcome		
Safety, frequency of adverse events (%)	Safety Questionnaire (Adapted for Adults from [35])	T_0, T_{26}, T_{52}
Satisfaction, overall score	TSQM[i] (Modified for dental) [36] and Satisfaction with new treatment for cavities (Modified for adults from [37])	T_{52} (for both satisfaction measures)
Moderators		
Sociodemographic, frequency (%)	NHANES[j] III [38]	T_0
Medical condition, frequency (%)	Common chronic health condition for adults 65+ (Adapted from [39])	T_0
Oral health behavior, overall score	Oral hygiene (Adapted from [40,41])	T_0
Oral health symptoms, overall score	Self-reported measures of current oral disease/tissue damage (Adapted from [42])	T_0

[a]T_0 = 0 week/Baseline visit/Baseline visual/tactile dental examination (Arm 1: SDF, Arm 2: ART + FV)

[b]T_{26}=26-week follow-up visit/Visual/tactile dental examination (Arm 1, Arm 2).

[c]SDF: silver diamine fluoride.

[d]ART: atraumatic restorative treatment.

[e]FV: fluoride varnish.

[f]T_{52}=52-week final visit/Visual/tactile dental examination (final).

[g]ICDAS: International Caries Detection and Assessment System.

[h]GOHRQoL: Geriatric Oral Health Quality of Life.

[i]TSQM: Treatment Satisfaction Questionnaire for Medication.

[j]NHANES: National Health and Nutrition Examination Survey.

Outcome

The primary outcomes are (1) clinical outcomes (caries lesion arrest [ICDAS activity code 1], inactive); and (2) participant-reported outcomes (tooth pain and hypersensitivity). Clinical outcomes will be assessed through dental examinations conducted by calibrated examiners. Participant questionnaire will assess patient-reported outcomes using validated instruments (Table 1). All primary outcomes will be measured at baseline and at 26 and 52 weeks.

The secondary outcomes are clinical (new caries lesions, ie, ICDAS lesion codes ≥3 on any surface that was previously sound), as assessed by dental examination; and

participant-reported outcomes (oral health quality of life) assessed through questionnaires. All secondary outcomes will be measured at baseline and at 26 and 52 weeks.

Other Moderator and Process Measures

The moderator variables include questions regarding sociodemographics [43], medical/physical conditions [44], oral health behavior [40,41], and oral health symptoms [42] that will be collected at baseline (prior to treatment) through the participant questionnaire. The process outcomes include questions regarding safety [35] assessed via a measure that will be collected at pretreatment and after treatment following the baseline treatment, and at 26 and 52 weeks; and satisfaction survey [36,37] with the treatment assessed after the exit visit at 52 weeks.

Study data will be collected and stored using the REDCap Electronic Data Capture platform hosted by Case Western Reserve University. The study staff use tablet computers for on-site data entry.

Fidelity Checks

The study staff members who will facilitate recruitment, scheduling, and data collection will attend a 2-day in-person training on the conduct of the study protocol and logistics. Specialized training in interviewing older adults will also be included. In-class training incorporates the topics of human subject protection, good clinical practice, and the study protocol. Study staff members will be monitored through periodic data audits and through direct observation of calls and recruitment activities. Staff members will receive feedback on their performance and conduct including but not limited to these specific areas, adherence to protocol and good clinical practice. Corrective training will be provided as required.

Sample Size and Power Estimates

This study tests the hypothesis that simple medical treatment (Arm 1) is noninferior to typical dental treatment (Arm 2) for primary outcomes (caries arrest, tooth pain/hypersensitivity) and secondary outcomes (new decay, oral health quality of life) at 52 weeks after treatment. For continuous outcomes power was computed using a variance correction (ie, variance inflation factor) to take into account possible correlations of outcomes within cluster. All computations of required effective samples sizes (or corresponding power) were done using the PASS 2005 software. For binary outcomes, a specialized program for cluster randomization (a noninferiority test comparing two proportions) was used.

The first primary outcome tooth pain was defined as change in pain (based on a 100-mm visual analog pain scale, where a higher score indicates worse pain) from baseline to 1 year. A mean difference of 0 between the SDF and ART + FV arms, and noninferiority to be within a margin (mean difference) of 8 between the SDF and ART + FV arms were considered, and based on prior literature we also assumed a common standard deviation of 25 [45]. Further, an average of 25 patients recruited per site, an intraclass correlation of 0.01 (based on prior studies and literature for similar populations) [46,47], and a conservative 15% dropout rate (based on prior studies) were considered including the possibility of deaths among participants. The use of a .025 α-level one-sided *t* test to test the null hypothesis of inferiority versus the alternative hypothesis of noninferiority (as defined above) in 11 sites per treatment group (corresponding to 275 subjects per treatment group or 550 in total) will provide an estimated 89% power to conclude noninferiority.

A second primary outcome is arrest rate. Previous data [19,48] show a high arrest rate (of around 90%) for ART + FV. A similar arrest rate for biannual application of SDF is expected [23]. For the power calculation, the unit of analysis was assumed to be the person, and considered the binary outcome of *arrest*, which is defined as all lesions for an individual being arrested. An equal (person-level) arrest rate of 90% for the ART + FV and SDF groups, and noninferiority to be within a margin (difference in arrest proportions for ART + FV versus SDF) of 0.09 were considered. With the same assumptions as before using a .025 α-level one-sided *z* test, the targeted sample size of 275 subjects in 11 sites per treatment group will provide an estimated 85% power to conclude noninferiority.

Randomization and Blinding

Randomization is at the level of the cluster (housing facility) for logistical efficiency, that is, we require supplies and personnel only for one intervention (rather than both) at each site. In addition, having only one intervention at each site will greatly reduce the potential for error (mistakenly giving the wrong treatment) that could otherwise occur with people at the same site assigned to different treatments. Furthermore, keeping the same treatment at each site reduces chances of *contamination* (ie, participant discussing their treatment with others). Particularly as one of the primary endpoints (self-reported pain/sensitivity) is subjective, it is important, in a context where blinding is not possible, to minimize the possibility that participants may perceive, through communication with others, that the treatment they are receiving is inferior or superior.

Additionally, stratified cluster randomization will be used, that is, a block (constrained) randomization approach in which balance over treatments is assured for 2 key cluster-level (stratification) variables, namely, facility size (>100 versus ≤100 residents) and geographic location (Cuyahoga County vs other). While the randomization is at the housing level, the study objectives, interventions, and primary outcomes all pertain to the individual level.

Study participants are blinded to the study group. Study staff will be blinded at the time of recruitment and obtaining consent.

Planned Analysis: Primary and Secondary Outcomes

Each primary outcome will be compared between the SDF and ART + FV groups. For tooth pain, a 95% CI based on a *t* test for the difference in mean responses (SDF minus ART + FV) will be computed. If the CI lies within the interval (–∞, 8), we may conclude *noninferiority* of SDF relative to ART + FV treatment. The CI may secondarily be examined to assess possible superiority of one intervention over the other. For arrest rate, a 95% CI for the difference in rates (based on a *z* statistic) will be computed. If the CI lies within the interval (–0.09, 1), we may conclude *noninferiority* of the SDF relative to ART + FV treatment. As above, possible superiority of one intervention

over the other may also be assessed. For other outcomes, we will also compute 95% CI for differences in means (or proportions for binary outcomes). These secondary outcomes will be assessed in an exploratory manner for possible superiority or inferiority based on appropriate margins.

We will seek to corroborate initial results using a generalized estimating equation (GEE) approach. For each outcome, a GEE (marginal) model will be fitted that includes a treatment indicator and prognostic variables (including sociodemographic variables, medical conditions, and oral health behaviors). Appropriate link functions (eg, logit link for binary outcomes and identity link for continuous outcomes) will be specified and an exchangeable working correlation matrix will be used to allow for correlations within site. The arrest outcome will be analyzed as a binary outcome (as described in the "Sample Size and Power Estimates" section), and secondarily as the number of arrested lesions assuming an appropriate distribution (eg, negative binomial) and link function (eg, log link). Robust *t* tests with correction for a small number of clusters [49] will be used to test for treatment effects and corresponding 95% CIs computed.

Secondarily, the above GEE approach will be extended to analyze the repeated (baseline and 26 and 52 week) measures for each outcome. The models for each outcome will include the same prognostic variables as before, as well as time and a time × treatment interaction, and will allow for correlations among the repeated measures (eg, using a first-order autocorrelation structure). If a substantial within-facility correlation is found, the need to incorporate facility as a second cluster level (within which a person [ie, the first cluster level] is nested) will be assessed. To compare trends over time for the 2 interventions, estimation and testing (via a robust *t* test) for the interaction term will be done. If the use of 2 cluster levels is not found to be feasible in the GEE approach, a generalized mixed effects model approach will be considered.

Dissemination

The study results will be disseminated through local and national conferences, scientific publications, and channels established by a 11-member stakeholder engagement group established for this project. For local and city levels, dissemination will occur through presentations, workshops, and educational programs conducted in community organizations. At the state level, results will be shared with the Ohio Department of Health, Medicaid policymakers, and third-party payers who can revise reimbursement policies. Nationally, Housing and Urban Development (HUD) will create flyers to be distributed to their housing facilities and share results with other states. All stakeholder partners have suggested sharing the results on their organization's respective webpages and newsletters, which reach large national, state, and local audiences.

Data Sharing Statement

The nonidentified data files, data dictionary, and supporting documentation will be available without restriction by application to the project biostatistician.

Results

Recruitment started in October 2019 and is currently ongoing (expected to be until the end of 2021). All follow-up intervention and data collection will be completed by the end of 2022. Final results are expected in June 2023.

Discussion

Overview

Dental practitioners lack robust guidance and standards of care for the treatment of older adults. The ability to provide treatment and the treatments themselves are impacted by the consequences of multiple medical problems, physical frailty, and dementia. Access is limited by the ability to pay. Dentists typically apply treatments developed for younger, healthier individuals, with predictably poor results. An article on the dental woes of an aging population [50] best summarizes this dilemma. This report relates an anecdote in which a public health dentist recalls a lecture given 20 years earlier on geriatric treatment during which the speaker presented slides of a patient with substantial evidence of previous treatment with excellent crowns and fillings. However, with gum recession, inflammation, and caries they had led to failure of the fillings and crowns. The patient was a retired dentist who was knowledgeable and had taken care of his teeth throughout his life, but medical problems, side effects of medications, and frailty took their toll. Conventional treatment with a drill was not an option in this case nor is it for many other older adults. The article concludes that with a growing geriatric population, a new standard of dental care was urgent. Nonsurgical treatments such as SDF and ART and FV are effective caries management strategies for older adults that address many of the limitations of traditional treatments.

Our study is a comparative effectiveness study of 2 nonsurgical treatments for addressing both root and coronal caries outcomes in older adults. Previous studies outside of the United States have mainly focused on the prevention and arrest of root caries lesions in community-dwelling older adults [19,21-23]. Both SDF and ART are two relatively inexpensive, evidence-based nonsurgical treatments that can be provided by dental hygienists (dental paraprofessionals) in most states outside of traditional dental clinics to address the unique oral health needs of community-dwelling older adults.

This study adds further to existing knowledge by addressing patient-reported outcomes such as pain and hypersensitivity that are of importance to older adults, as they affect their overall oral health quality of life. In our prior study of older adults living independently in 16 subsidized housing facilities in Northeast Ohio, 62% of the participants reported that their perceived tooth condition was fair/poor [6] with 40% reporting tooth pain and 54% tooth sensitivity. Both treatment strategies have the ability to kill plaque bacteria and strengthen the tooth surface [24-27] and thus address pain and sensitivity. SDF, in particular, has been cleared by the FDA as a tooth desensitizer.

This comparative trial can also provide needed evidence regarding the effectiveness of these interventions in community-based settings (ie, for public health purposes).

Currently, there are no community-based public health interventions for older adults like those for children. For any dental caries preventive/treatment intervention to be useful on a population level, 5 presumed attributes are necessary: pain and infection control, simplicity of use, cost affordability, minimal personnel time and training, and noninvasiveness [51]. Potentially, these nonsurgical interventions have these attributes and can address the limitations of the current clinic-based dental care delivery system which is expensive and ill adapted [52].

Generalizability

The state requirements for supervision vary considerably. The results of this trial may be applicable to settings in which dental hygienists, or perhaps dental therapists, are permitted to provide services under general supervision outside of traditional clinics and practices. The results are limited by the necessity to select particular dental materials based on our current assessment of their practicality and ease of application. Other materials may behave differently as industry is constantly innovating and changing the materials. Nevertheless, evidence for this class of treatment alternatives can result in more robust treatment guidelines and standards that are broadly generalizable.

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Conflicts of Interest

PM is a director of Advantage Silver Dental Arrest, LLC. Advantage has a marketing agreement with Elevate Oral Care for Advantage Arrest. PM will not interact with participants or have any direct contact with the study data. The other authors declare no conflict of interest.

Multimedia Appendix 1
Study flyer.
[PNG File , 394 KB - resprot_v9i9e17840_app1.png]

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Abbreviations

ART: atraumatic restorative treatment
FV: fluoride varnish
GEE: generalized estimating equation
GIC: glass ionomer cement
ICDAS: International Caries Detection and Assessment System
SDF: silver diamine fluoride

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Protocol

Evaluation of a Package of Behaviour Change Interventions (Baduta Program) to Improve Maternal and Child Nutrition in East Java, Indonesia: Protocol for an Impact Study

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Abstract

Background: Over the past decade, the prevalence of stunting has been close to 37% in children aged <5 years in Indonesia. The Baduta program, a multicomponent package of interventions developed by the Global Alliance for Improved Nutrition, aims to improve maternal and infant nutrition in Indonesia.

Objective: This study aims to assess the impact of the Baduta program, a package of health system strengthening and behavior change interventions, compared with the standard village health services on maternal and child nutrition.

Methods: The impact evaluation uses a cluster randomized controlled trial design with 2 outcome assessments. The first uses cross-sectional surveys of mothers of children aged 0-23 months and pregnant women before and after the interventions. The second is a cohort study of pregnant women followed until their child is 18 months from a subset of clusters. We will also conduct a process evaluation guided by the program impact pathway to assess coverage, fidelity, and acceptance. The study will be conducted in the Malang and Sidoarjo districts of East Java, Indonesia. The unit of randomization is the subdistricts. As random allocation of interventions to only 6 subdistricts is feasible, we will use constrained randomization to ensure balance of baseline covariates. The first intervention will be health system strengthening, including the Baby-Friendly Hospital Initiative, and training on counseling for appropriate infant and young child feeding (IYCF). The second intervention will be nutrition behavior change that includes *Emo-Demos*; a national television (TV) advertising campaign; local screening TV spots; a free, text message service; and promotion of low-cost water filters and hygiene practices. The primary study outcome is child stunting (low length-for-age), and secondary outcomes include length-for-age Z scores, wasting (low weight-for-length), anemia, child morbidity, IYCF indicators, and maternal and child nutrient intakes. The sample size for each cross-sectional survey is 1400 mothers and their children aged <2 years and 200 pregnant women in each treatment group. The cohort evaluation requires a sample size of 340 mother-infant pairs in each treatment group. We will seek *Gatekeeper* consent and written informed consent from the participants. The intention-to-treat principle will guide our data analysis, and we will apply Consolidated Standards of Reporting Trials guidelines for clustered randomized trials in the analysis.

Results: In February 2015, we conducted a baseline cross-sectional survey on 2435 women with children aged <2 years and 409 pregnant women. In February 2017, we conducted an end-line survey on 2740 mothers with children aged <2 years and 642

pregnant women. The cohort evaluation began in February 2015, with 729 pregnant women, and was completed in December 2016.

Conclusions: The results of the program evaluation will help guide policies to support effective packages of behavior change interventions to prevent child stunting in Indonesia.

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KEYWORDS

infant; feeding behavior; diet, food, and nutrition; growth disorders; undernutrition; nutrition during pregnancy; water treatment

Introduction

Background

Over the past decade in Indonesia, there has been little change in child stunting, with the national prevalence of stunting estimated as 37% of children aged under 5 years [1,2]. This high level of growth failure has profound adverse consequences for the physical and economic development of affected children, their communities, and the country overall [3-7]. Growth faltering among Indonesian children starts in utero and is associated with low maternal height and poor nutritional status [8-15]. Among children in Indonesia, as elsewhere, 2 major determinants—undernutrition and infections—broadly account for postnatal deterioration in growth [10,15-20]. In studies examining risk factors for child stunting in Indonesia, lower maternal education and household wealth, including lower expenditure on foods from animal sources, are associated with a higher prevalence of child stunting [15,18,19,21].

Presidential Decree Number 42/2013 on The National Movement for the Acceleration of Nutrition Improvement prioritized the improvement of nutritional status in the first 1000 days of life, with the stunting of children aged <5 years as a key indicator. The decree addresses 4 main strategies. The first is to make nutritional improvements as the mainstream of the development plan. The second is building capacity and increasing human resource competence to respond to nutritional needs in all sectors. The third is to promote effective evidence-based interventions to improve nutrition. The fourth is increasing community participation in nutrition programs. The Government of Indonesia prioritized stunting reduction as part of the Ministry of Health Strategic Plan 2015-2019 and aimed to reduce the prevalence of stunting among children aged <2 years from 33% in 2013 to 28% in 2019 [22].

In Indonesia, the public health system is decentralized and is the responsibility of the district and municipal governments. They manage health services through the District Health Office and deliver primary health care services through community health centers (*Puskesmas*). Civil society also actively participates in the health sector through a community initiative called the integrated village health post (*Posyandu)*. It consists of community volunteers (health cadres), trained by village midwives, or other community health center staff. The health cadres assist with preventive health services, including nutrition education to pregnant women and caregivers of children aged 0-59 months.

In 2014, the Ministry of Health requested the Global Alliance for Improved Nutrition (GAIN) to support the Malang and Sidoarjo districts in East Java to reduce child stunting. Subsequently, GAIN initiated the *Baduta* (means children aged <2 years in Indonesian) program with funding from the Ministry of Foreign Affairs of the Netherlands and in collaboration with Save the Children, Paramitra Foundation, and PT Holland for water (Nazava). The experience and recommendations generated through the Baduta program will inform on efforts to improve nutrition and prevent stunting nationally in Indonesia. GAIN invited the University of Sydney, in collaboration with the Centre for Health Research, Universitas Indonesia, and the London School Hygiene and Tropical Medicine to conduct a comprehensive theory-driven evaluation designed to learn about the factors affecting program delivery and the achievement of the impact of the interventions [23,24]. This paper describes the study protocol for the impact and process evaluations of the Baduta program.

Objectives

The Baduta study aims to assess the impact of a package of health system strengthening and behavior change interventions on maternal and child nutritional status compared with the standard, integrated village health post services. The primary outcome in the cross-sectional evaluation will be the prevalence of low length-for-age (<-2 Z scores) in children aged <2 years in each treatment group, whereas in the cohort evaluation, it will be the mean length-for-age Z scores in each treatment group. The secondary outcomes will include mean length-for-age Z scores, the prevalence of low weight-for-length (<-2 Z scores), child anemia (hemoglobin [Hb] <11 g/dL), indicators of infant and young child feeding (IYCF) practices, maternal and infant dietary intake, and use of iron and folic acid supplements by pregnant women.

Hypotheses

Primary Hypothesis

A package of behavior change interventions and health system strengthening activities delivered to a rural population in East Java, Indonesia, over 18 months will improve women's diet and iron supplementation in pregnancy, breastfeeding, and complementary feeding practices; promote hygienic food preparation; and promote use of clean drinking water. The interventions will reduce the prevalence of stunting (length-for-age Z score <-2 Z) in children aged 0 to 23 months by 6% (35% in the control group to 28.9% in the intervention group) as assessed in cross-sectional surveys, compared with

areas with only the routine integrated village health post services.

Secondary Hypotheses

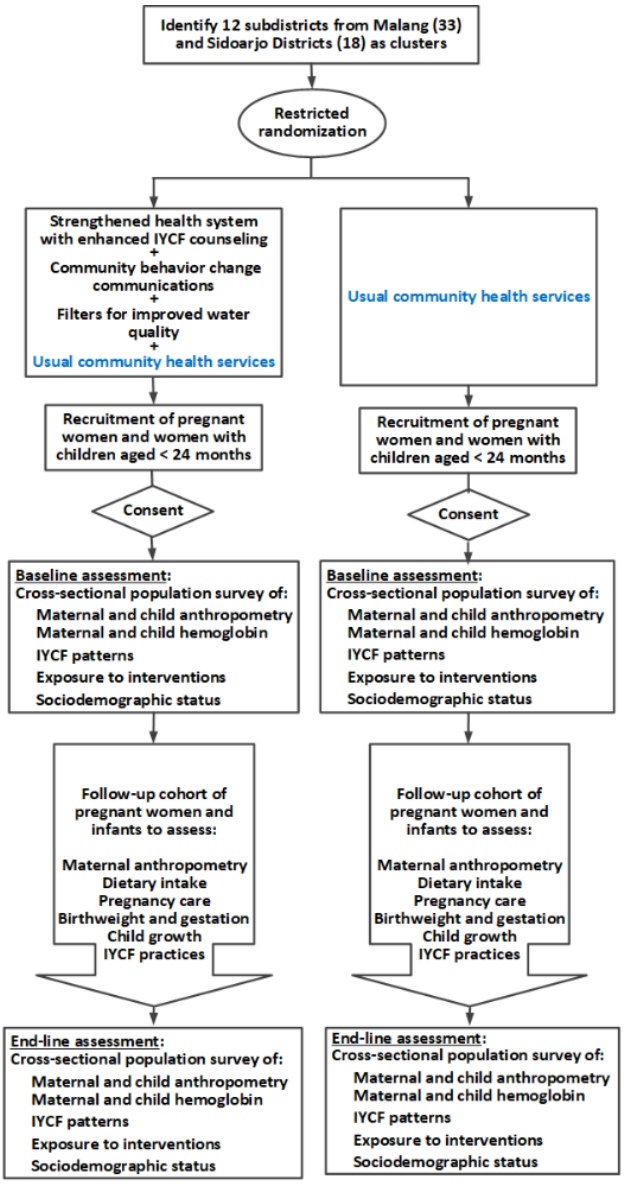
The interventions will (1) increase mean length-for-age Z scores, mean weight-for-age Z scores, and mean weight-for-length Z scores at 18 months in the cohort of children followed up longitudinally; (2) decrease the prevalence of low weight-for-age and low weight-for-length in baseline and end-line cross-sectional surveys; (3) decrease the number of children ill with diarrhea, acute respiratory illness, or fever in both cross-sectional and cohort assessments; (4) decrease the prevalence of anemia in pregnant women and children aged <2 years; (5) increase women's knowledge about appropriate breastfeeding practices; (6) increase median duration of exclusive breastfeeding and the percentage of women exclusively breastfeeding at 6 months and age-appropriate breastfeeding in children aged 0 to 23 months; (7) increase women's knowledge about appropriate complementary feeding including snacks; (8) decrease the percentage of children aged <2 years receiving snacks; (9) increase the percentage of children consuming ≥4 food groups at ages 6-8, 9-11, and 12-23 months in the end-line cross-sectional assessment and ages 7, 10 and, 17 months in children followed up in the cohort assessment; and (10) increase nutrient intakes, nutrient density, and dietary adequacy for children aged 6-23 months.

Methods

Study Design

The study is a probability impact evaluation [25] using a cluster randomized controlled trial with 2 parallel treatment arms. The design uses a superiority hypothesis, having one-to-one allocation of the treatments, 2 types of outcome assessments, and a process evaluation (Figure 1).

Figure 1. Diagram of the study design for the impact evaluation. IYCF: infant and young child feeding.



Cross-Sectional Survey Assessment

The first assessment approach will use repeated cross-sectional surveys of mothers of children aged 0-23 months and pregnant women at baseline before interventions commence and 2 years later at the end line, which is the best approach to assess the impact of the intervention on the stunting prevalence in the study population (population-level impact) [26]. In the cross-sectional surveys, we will collect information on socioeconomic and demographic characteristics, infant feeding practices including intentions of the mother to breastfeed and mother's self-efficacy with breastfeeding, child morbidity reported by mother/caregiver, contact with the health system and exposure to the interventions, maternal and child anthropometry, and maternal and child hemoglobin. We will assess the impact by comparing the change in the prevalence of key indicators between the treatment groups in children aged <2 years and pregnant women.

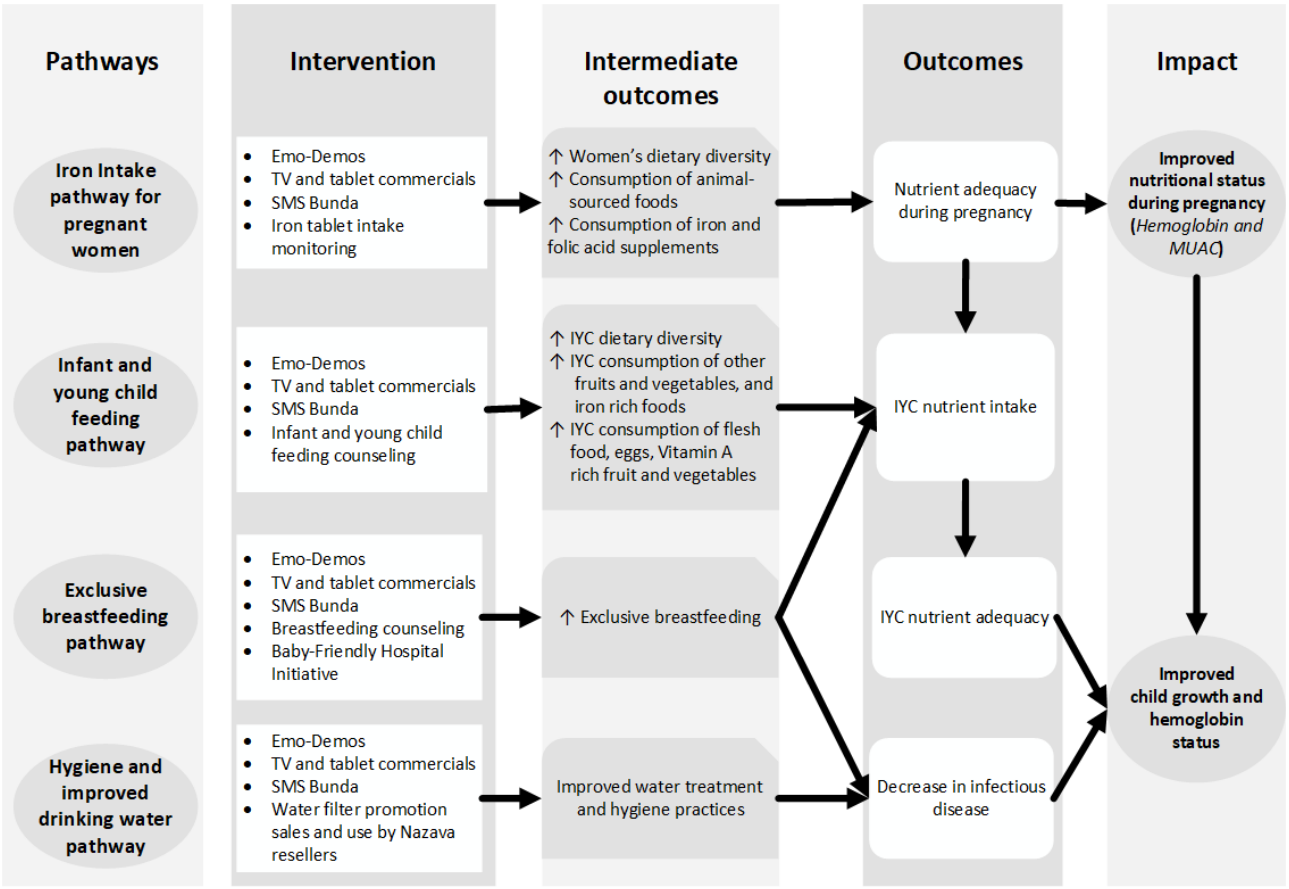
Cohort Study Assessment

The second will be a cohort study that will recruit pregnant women from a subset of study clusters and follow them from late in the third trimester of pregnancy until their child is 18 months old to examine the impact of the interventions on child growth at the individual level. This cohort study will allow us to examine subgroups for any modifying effects on the primary outcome, for example, the modifying effects of different levels of maternal education and household wealth on the impact of the intervention on the study outcomes. We will exclude women who are severely anemic (Hb<7 g/dL) or have chronic diseases such as tuberculosis, women who intend to migrate outside the subdistrict, infants born with a visible congenital defect, and multiple births (twins) from the cohort study.

Program Impact Pathways

The Baduta interventions should operate through 4 intervention pathways, as shown in the program impact pathway illustrated in Figure 2. The first pathway is to improve nutritional status during pregnancy by improving the nutrient adequacy of diets through increased consumption of foods from animal sources and iron and folic acid supplements. The second is to improve the nutrient adequacy of infant and young child diets through improved dietary diversity. The third is to reduce infectious diseases and improve nutrient intake through adherence to exclusive breastfeeding in the first 6 months of life. The fourth is to reduce infectious diseases through improved water and sanitation practices.

Figure 2. Impact pathways of the Baduta program interventions. IYC: infant and young child; TV: television.



Process Evaluation

During the delivery of the interventions, we will also conduct a process evaluation to assess the intervention input, output, and outcomes related to the program impact pathway and responses of the target populations to the intervention and contextual factors affecting the intervention. We will integrate and align the process evaluation with process monitoring of the implementers of the interventions.

Study Setting

We will perform the study in the Malang and Sidoarjo districts of East Java, Indonesia (see Multimedia Appendix 1—a map of East Java with the study districts marked), which had an estimated population of almost 2 million and 2.5 million in 2014, respectively. There are 350 villages in Sidoarjo and 390 villages in Malang. The population density of Sidoarjo (2891/km^2) is almost 4 times the population density of Malang (780/km^2) [27]. Sidoarjo is a peri-urban district, with 13% of households from urban areas, and most adults are employed as factory workers (36%) or providing public and private services (41%: trader, hotels, restaurant, and public institutions) [28]. Malang is a rural district, with 97% of households from rural areas, and most adults are employed as farmers (33%) or providing public and private services (34%: traders, hotels, restaurants, and public institutions) [29]. On the basis of the annual nutrition surveillance data from the Ministry of Health, there are 24% of children aged <5 years who are stunted in Sidoarjo and 31% in Malang. Approximately two-thirds of the children aged <5 years in Malang and a half in Sidoarjo attend integrated village health posts for weight monitoring [28,29].

There are 51 subdistricts available for the study (33 in Malang and 18 in Sidoarjo), with an average population of 86,000. On average, there are 1.3 community health centers in each subdistrict, and each covers a population of approximately 68,000 people. Within the catchment area of each community health center, there are, on average, 2.8 subcenters (*Pustu*) that cover 5 villages or about a population of 30,000. Primary health care outreach to the community uses monthly integrated village health posts organized by local female health volunteers who coordinate with the community health center staff and village midwives. Village midwives are trained midwives who reside in 1 village within the community health center catchment area and are part of the service network. The village midwives' program is part of the government's efforts to accelerate the improvement of community health, particularly concerning maternal and child health. The roles and responsibilities of village midwives include maternal and child health, family planning services, health promotion, and preventive services as well as early detection and initial treatment for maternal and child health conditions, including undernutrition.

Cluster Selection and Design of Randomization

The unit of randomization for the study will be subdistricts, selected by the authors to prevent contamination as they will deliver the health system strengthening interventions through the subdistrict community health centers. It will only be feasible to randomize a limited number of subdistricts to the new interventions versus the standard programs. As we will be limited to 12 subdistrict clusters (6 intervention and 6 usual programs), it will not be possible to use simple randomization to allocate them randomly to the intervention or control groups.

We will use constrained randomization [30,31] to ensure a balanced distribution of covariates in the study treatment groups because of the limited number of subdistrict clusters in which it is feasible to conduct the study. There are 33 subdistricts in Malang and 18 subdistricts in Sidoarjo. We will exclude subdistricts with similar ongoing projects and small subdistricts (population <70,000), leaving 24 subdistricts eligible for the study.

We will conduct hierarchical cluster analysis on the 24 eligible subdistricts using data for each district from the 2011 Village Potential Statistics (Pendataan Potensi Desa/Kelurahan) data set and local health surveillance data. We will use indicators of household economic status, access to health care, and prevalence of undernutrition in children to identify a group of similar subdistricts. We will select a group of 12 of the most similar subdistricts and construct a list of the 924 possible combinations of 6 intervention subdistricts and 6 comparison subdistricts. We will perform the analyses for constrained randomization with SAS 9.2 (SAS Institute Inc) using an algorithm developed by Chaudhary and Moulton [32].

We will select combinations of intervention and comparison subdistricts with balanced covariates, as measured by a difference in (1) the average distance of the neighborhood to the closest community health care center with a cutoff value for balance <0.5 km, (2) the coverage of children weighted at village health posts with a cutoff value for balance <5%, (3) the prevalence of underweight children (weight-for-age less than –2 Z score from growth monitoring charts) with a cut off value for balance <2.5%, (4) the ratio of village health posts to the total population with a cutoff value for balance <1.6/10,000 population, and (5) the percentage of low-income families who have a local government Certificate of Disadvantage (Surat Miskin/Surat Keterangan Tidak Mampu) with a cutoff value for balance <5%. Using simple random sampling, we will select one of the balanced combinations of subdistricts for allocation of the study interventions.

Formative Research and Pilot Studies

Before designing the Baduta program, GAIN conducted formative research to identify delivery platforms, create communication strategies and frame messages, and develop communication materials [33]. The GAIN staff and a research team from the London School of Hygiene and Tropical Medicine, London, United Kingdom, and the Regional Centre for Food and Nutrition, Southeast Asian Ministers of Education Organization (SEAMEO-RECFON), Jakarta, Indonesia, conducted formative research and a pilot study of the Healthy Gossip Movement (Gerakan Rumpi Sehat) intervention [33] to determine whether a communication strategy that focused on strong behavioral handles rather than educational messages would be effective in changing nutritional behavior. The Baduta project team developed 12 participative and demonstrative activities for delivery in community settings called *Emo-Demos*. The *Evo-Eco* theory [34] underpins these activities, which are grounded in the psychological and environmental determinants of behavior. This approach suited a community setting where nutrition knowledge was high, but the adoption of healthy nutritional behaviors was poor [35]. The pilot study found a greater improvement in dietary diversity when messaging based on emotional drivers of behavior change was channeled through both mass media TV adverts and *Emo-Demo* community activities [33]. We used these 2 interventions in the package of behavior change interventions for the Baduta program.

Description of the Baduta Program Interventions

The interventions will primarily aim to strengthen the existing activities delivered through the public health system to promote recommended nutrition practices for pregnancy, breastfeeding, and complementary feeding. We will implement the following activities in the intervention subdistrict clusters during the study.

Health System Strengthening Interventions

In the first health system strengthening intervention, Save the Children will launch the implementation of the Baby-Friendly Hospital Initiative (BFHI) [36] in the public sector district and municipal hospitals and birthing centers at the community health centers in the intervention subdistricts. The World Health Organization (WHO) and the United Nations Children's Emergency Fund (UNICEF) jointly conceived the BFHI in 1991 as a strategy to improve breastfeeding rates worldwide. A hospital or birth center can receive Baby-Friendly designation if they show compliance with the Ten Steps to Successful Breastfeeding [36].

In the second health system strengthening intervention, Save the Children will train village midwives, health workers, and integrated village health post cadres on counseling for appropriate IYCF using the Indonesian Ministry of Health adaptation of the WHO/UNICEF Community Infant and Young Child Feeding Counseling Package [37].

Behavior Change Interventions

We will employ 4 different behavior change interventions to address program outcomes, as shown in the program impact pathway (Figure 1). We have developed behavior change communications using the Behavior Centered Design theory and employed emotional drivers of behavior change rather than education-focused messaging [33].

The first will be 12 participative and demonstrative behavior change activities called *Emo-Demos*, developed by the London School of Hygiene and Tropical Medicine, London, United Kingdom, and GAIN [33], which are based on the psychological and environmental determinants of behavior. The Emo-Demos include topics on nutrition during pregnancy (3 activities), breastfeeding (3 activities), care during pregnancy (1 activity), complementary feeding issues (4 activities), and handwashing (1 activity; see Multimedia Appendices 2 and 3 for details of Emo-Demos). The Paramitra Foundation will recruit and train village facilitators to train village midwives and health cadres to deliver Emo-Demos during monthly pregnant women classes and child growth monitoring at the integrated village health post.

The second will be a national TV campaign that will have 4 high-quality spots with messages on nutrition during pregnancy (1 spot), breastfeeding (1 spot), and complementary feeding issues (2 spots; see Multimedia Appendices 4 and 5 for a description of these TV spot messages). The TV spots will air on 5 national TV channels, and it will not be possible to contain them to only the intervention subdistricts. Village facilitators will also screen the TV spots using tablets during integrated village health post meetings and with people passing by during *street visits*.

The third will be the established SMS Bunda intervention, a free, text message service for pregnant women and postnatal mothers that aims to reduce maternal and infant mortality [38]. Midwives encourage women to access the service by registering their mobile number and the expected date of delivery at any time during pregnancy. Initially, in pregnancy, the women receive regular short messages about antenatal care. In the last month of pregnancy, the text message contains information related to the first days after childbirth for mother and baby, including information about early initiation of breastfeeding. In the first month of birth, the messages provide information about the health of mothers and newborns, including exclusive breastfeeding.

In the fourth intervention, GAIN will partner with a company, Nazava, to expand sales of low-cost water filters and promote appropriate water treatment and hygiene practices. Water filters are a low-cost and effective method to purify water that avoids costly fuels (wood or electricity) to boil water. Nazava's rural sales network in the Malang and Sidoarjo districts as well as trained resellers will market the filters and provide education sessions on water treatment and handwashing.

Description of Standard Primary Health Care Services

During the study, both the intervention and the comparison clusters will receive the standard primary health care services. Monthly integrated village health posts are the delivery platforms for the usual community health services that include child growth monitoring, food supplements, child immunizations, antenatal care, pregnancy classes, and family planning services. The local community, particularly the village health cadres, organize the integrated village health post services under the supervision of the community health center staff. The community health center staff, village midwives, and village health cadres deliver the services.

Evaluation Outcomes

Primary Outcomes

The primary outcome for the cross-sectional evaluation is the difference in the percentage of stunted (length-for-age<–2 Z scores) children aged 0-23 months between the intervention and the comparison groups at the baseline and end-line surveys. For the cohort evaluation, the primary outcome is the difference in the mean length-for-age Z scores between the intervention and the comparison groups every 3 months from birth to 18 months, as measured in the follow-up assessments.

Secondary Outcomes

The secondary outcomes for the cross-sectional evaluation include differences between the 2 treatment groups at the baseline and end-line surveys in the following: (1) the percentage of wasted (weight-for-length<–2 Z scores) children aged 0-23 months and their mean weight-for-length Z scores; (2) the percentage of children aged 0-23 months with low hemoglobin (Hb <11 g/dL) and their mean hemoglobin; (3) the number of events and the mean number of days the children are ill >2 weeks before interview with diarrhea, acute respiratory infections, and fever; (4) the percentage of children aged 0-23 months who are ever breastfed, are breastfed with an hour of

birth, are given prelacteal feeds, are exclusively breastfed in the first 6 months of life, continue breastfeeding at 1 and 2 years, and are age appropriately breastfed; (5) the percentage of children aged 6-23 months with minimum dietary diversity, minimum meal frequency, minimum acceptable diet, and frequency of consumption of 7 food groups and iron-rich foods; (6) the percentage of children aged 6-23 months consuming snacks the day before the interview; (7) the mean intake of food energy, protein, carbohydrate, fat, and selected micronutrients from complementary foods and the micronutrient density of the complementary feeding diets compared with desired levels at 6-8, 9-11, and 12-23 months of age; (8) the percentage of children aged 12-23 months at risk of inadequate nutrient intake; (9) the percentage of mothers with appropriate knowledge about IYCF; and (10) the percentage of mothers with high self-efficacy for breastfeeding.

The secondary outcomes for the cohort evaluation include differences between the 2 treatment groups in the following: (1) the percentage of wasted (weight-for-length<–2 Z scores) children and their mean weight-for-length Z scores every 3 months from 3 to 18 months; (2) the percentage of children with low hemoglobin (Hb <11 g/dL) and their mean hemoglobin at 18 months of age; (3) the number of events and the mean number of days the children are ill >2 weeks before interview with diarrhea, acute respiratory infections, and fever from birth to 18 months; (4) the percentage of children who are ever breastfed, are breastfed within 1 hour of birth, are given prelacteal feeds, and are exclusively breastfed each month from birth to 6 months; (5) the median maternal breastfeeding self-efficacy score and the percentage of mothers with high self-efficacy for breastfeeding at 7 days and 3 and 6 months postpartum; (6) the percentage of children with minimum dietary diversity, minimum meal frequency, and minimum acceptable diet at 7, 10, and 17 months of age; (7) the percentage of children consuming snacks within 1 hour of meals and the contribution of snacks to energy intake at 6-8, 9-11, and 16-18 months of age; (8) the mean intake of food energy, protein, carbohydrate, fat, and selected micronutrients from complementary foods and the micronutrient density of the complementary feeding diets compared with desired levels at 6-8, 9-11, and 12-23 months of age; (9) the percentage of women receiving and consuming iron and folic acid supplements during pregnancy; and (10) the percentage of women pregnant in their third trimester meeting minimum dietary diversity and at risk of inadequate nutrient intakes.

Outcome Measurements

In the cross-sectional assessment at baseline and end-line surveys, we will measure the following factors or indicators: social, economic, and demographic characteristics; infant feeding practices; child morbidity; contact with the health system; and exposure to the interventions. We will also measure maternal and child anthropometry and hemoglobin status.

In the cohort assessment, we will conduct repeated data collection on social, economic, and demographic characteristics; infant feeding practices; maternal and child dietary intake; child morbidity; contact with the health system; and exposure to the interventions. We will also conduct repeated measurements of maternal and child anthropometry and child hemoglobin status at 18 months.

Anthropometry

Trained field workers will collect measurements of weight, recumbent length in infants, height in mothers, and mid-upper arm circumference in pregnant women using standard methods and equipment [39,40]. We will standardize the measurements of the anthropometry field workers using established methods before and during data collection [39]. In both the cross-sectional and cohort evaluations, 2 field workers will collect duplicate measurements of the weight and length of children aged <2 years. The field workers will take a third measurement if the difference between the first 2 measurements exceeds a predetermined allowable limit (see details below).

We will calculate the Z scores for infant length-for-age and weight-for-length using the 2006 WHO Child Growth Standard [41], and we will define stunting as a low length-for-age or <−2.00 SD from the reference mean and wasting as low weight-for-length or <−2.00 SD. We will collect mid-upper arm circumference from pregnant mothers and define it as low if <23 cm [42].

The field workers will collect all anthropometry data using in-field digital data capture on tablets with routines that immediately calculate Z scores and provide them with a warning about extreme values and the need for remeasurement to check for potential errors (ie, if first and second measurement differed by >0.7 cm for length and by >0.1 kg for weight). We will refer to children with very low weight-for-height (Z score<−3) to their local community health center for assessment and treatment of severe acute malnutrition.

Birth Weight and Duration of Gestation

In the cross-sectional assessment, we will ask mothers of children aged <2 years to recall the birth weight and ask them to describe their infant's birth size using the same question as in the Indonesian Demographic and Health Survey (DHS) [43]. There will be no estimate of the duration of gestation. In the cohort assessment, we will measure birth weight within 72 hours after birth. We will estimate the duration of gestation using the mother's report of the first date of her last menstrual period.

Hemoglobin

In the cross-sectional evaluation, we will assess hemoglobin in all women and children. However, in the cohort evaluation we will assess hemoglobin from children at 18 months and mothers during pregnancy. We will collect capillary blood samples and measure hemoglobin using a portable hemoglobinometer (Hemocue). We will refer mothers with a hemoglobin level <12 g/dL and children with a hemoglobin level <11 g/dL to their local community health center for assessment and treatment.

Child Morbidity

In the cross-sectional and cohort assessments at the scheduled visits (Figure 3), trained interviewers will record maternal recall of symptoms from the preceding 2 weeks of common childhood illnesses (diarrhea, cough, and fever) using the standard Indonesian DHS questions.

Figure 3. Schedule of enrollment, interventions, and assessments for cohort evaluation. X: indicates activity occurred at given visit or life cycle stage; lines mark the duration of the interventions; 24 HR: 24-hour dietary recall.

	Study Period															
Study stage	Cluster allocation	Baseline	Follow-up visit													Closeout
Calendar time	January to February 2015	March to April 2015	April 2015 to February 2017													
Life cycle stage			Postpartum within 72 hrs	Postpartum 7 days	1 month	2 months	3 months	4 months	5 months	6 months	7 months	8 months	9 months	12 months	15 months	18 months
Visit number		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Enrolment:																
Allocation	X															
Eligibility screen		X														
Informed consent		X														
Interventions:																
Health system strengthening		—	—	—	—	—	—	—	—	—						
Behavior change interventions		—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Assessments:																
Identification		X														
Household information		X														
Pregnancy knowledge		X														
Breastfeeding intention		X														
Infant feeding knowledge		X														
Food security		X														X
Birth outcome and delivery services				X												
Antenatal care				X												
Breastfeeding practices				X												
Complementary feeding practices					X	X	X	X	X	X			X	X	X	X
Utilization of Posyandu							X			X			X	X	X	X
Immunizations														X		
Exposure to Baduta intervention					X		X			X			X	X	X	X
Child morbidity					X	X		X	X							
Mother 24HR dietary intake		X								X						X
Child 24HR dietary intake										X			X			X
Anthropometry - mother		X					X									X
Anthropometry - child			X		X		X			X			X	X	X	X
Hemoglobin assessment - mother		X														
Hemoglobin assessment - child										X						X

IYCF

In both the cross-sectional and cohort evaluations, we will collect information about IYCF using an interviewer-administered questionnaire on breastfeeding and general complementary feeding practices. In the cross-sectional evaluation, trained interviewers will ask questions about infant feeding practices based on questions from the Indonesian DHS that allow estimation of the standard WHO IYCF indicators [44]. These IYCF questions will include the timing of initiation of breastfeeding; current breastfeeding status; use of bottles for feeding; current use, timing, and introduction of other liquids and solid foods; meal frequency; and consumption of food groups in the previous 24 hours and week before the interview. We will also collect 24-hour dietary recalls (24-HR), which will be used to assess indicators of IYCF (see the Dietary Intake Data section).

In the cohort assessment, we will administer the questions about IYCF at the same time as we collect the anthropometric data, that is, soon after birth, every month in the first 6 months, then every 3 months until they are 18 months of age.

We will estimate indicators of IYCF according to the WHO indicators for assessing IYCF practices [44], including early initiation of breastfeeding, exclusive breastfeeding, predominant and continued breastfeeding, bottle-feeding practices, dietary diversity score, meal frequency, minimal acceptable diet, and timing of initiation of complementary feeding.

Information will be collected about mothers' intentions to breastfeed their infants when they are pregnant. We will assess the mothers' self-efficacy with breastfeeding using the breastfeeding self-efficacy short questionnaire developed by Dennis [45], which is a 14-item instrument aimed at measuring breastfeeding confidence, at birth and at 1, 3, and 6 months postpartum.

Dietary Intake Data

Quantitative dietary intake data will be collected using 4-pass 24-HR. In the cross-sectional evaluation, we will collect it at baseline and end line from pregnant women and infants aged 6-23 months, whereas in the cohort assessment, we will collect it from mothers during pregnancy (third trimester) and from infants at 7, 10, and 17 months of age. Paper-based data collection was used to collect dietary data in the cross-sectional surveys and for the pregnant women in the cohort study, whereas digital data capture was used to collect the 24-HR from children in the cohort study.

For each target group and data collection period, 24-HRs will be proportionately collected on all days of the week to account for any day of the week effects on dietary intakes. In subsamples of pregnant women and infants aged 12-23 months, we will collect repeated 24-HRs on nonconsecutive days (n=40 per target group per data collection period) to adjust nutrient intake distributions for intrasubject variability [46] when estimating the percentage at risk of inadequate nutrient intakes.

We will collect all 24-HRs in the participants' homes by trained interviewers using standardized methods [46]. Briefly, in the *first pass*, each respondent will be asked to recall all foods and beverages consumed by herself (or her child) during the preceding day. In the *second pass*, for each food and beverage listed, we will record details about the time of consumption, the food and beverage (brand names, ingredients, and cooking methods), and any food items added (eg, sugar added to tea). In the *third pass*, we will ask the respondents to estimate the amount they (or their child) consumed, after probing for leftovers. Portion sizes will be quantified by weighing the indicated amounts of real foods, photographs, food models, or

by the number of standard units consumed. We will develop a standard portion size manual to ensure that all interviewers use consistent methods. We will record recipes, including the amounts of raw food used in the recipe, the cooking method, and the total amounts cooked and consumed. In the *fourth pass*, the interviewers will review the dietary data for completeness, and they will ask whether the previous day's diet represented a typical day and, if not, how it differed from usual, and for infants, whether they were breastfed on the previous day.

Dietary Data Processing

Dietary data will be collected using either a paper-based questionnaire or an in-field digital data capture on tablets for multiple-pass 24-HR that is under development. The digital data capture system saves data processing time and reduces errors by ensuring that probes and food portion size estimations are standardized. At the end of each data collection day, all dietary data will be checked for completeness by the team supervisor. Paper-based questionnaires will be entered into computer files with special-purpose data entry screens, and digitally captured questionnaires will be downloaded directly to a central server. The 24-HR records from both sources will be reviewed by trained nutritionists to monitor data quality and to select the appropriate food composition for foods not linked to an existing food composition item. We will monitor dietary data quality by applying a plausible energy range for children (by age group and breastfeeding status) to identify energy under- and over-reporting.

Process Evaluation

Process evaluation of the Baduta study aims to assess program coverage, fidelity, and acceptance by the intended target population, guided by the program impact pathway, and to demonstrate plausibility and the attribution of impacts to the intervention. We will emphasize the 4 program impact pathways that include knowledge adoption of (1) exclusive breastfeeding, (2) IYCF practices, (3) iron intake pathway, and (4) knowledge adoption of household water treatment and safe storage and hand washing. In the process evaluation, we will collect data about the interventions attached to these 4 pathways, such as the BFHI, breastfeeding and complementary feeding counseling, emotional demonstration (Emo-Demo), and enhanced water treatment through the household-level promotion of Nazava water filters.

We will use mixed methods to collect process evaluation data. The qualitative methods will include semistructured interviews with women participating in the intervention, health workers (midwives, nurses, village midwives, cadres, nutritionists, and doctors), managers (the head of the community health center and the head of midwives), and intervention implementers (Project Manager, Monitoring Officer, and Field Officer of Save the Children; Director, Project Manager, Monitoring Officer, and Subdistrict Coordinator of Paramitra; and Project Manager, Safe Eater Consultant, and Save Water Entrepreneur of Nazava); a structured questionnaire survey of the water filter users; and observation of Emo-Demo sessions. Apart from these primary data, we will use secondary data from the project monitoring records maintained by Save the Children, Paramitra, and Nazava.

The field research team will consist of nutritionists, anthropologists, and psychologists who have previous experience in qualitative research and speak the local language. The investigators from the University of Indonesia, SEAMEO-RECFON, and the University of Sydney will train the field research team in qualitative data collection, data organization methods, and survey methods. They will be involved in finalizing the data collection tools that will be pretested before data collection. We will purposively select a sample of the clusters from the evaluation study to collect the process evaluation data.

Sampling Design and Sample Size

Sample Size

We estimated the targeted sample size for the study using the following assumptions: (1) in the 51 subdistricts in the Malang and Sidoarjo districts, there is a total population of approximately 4.4 million, with an average of approximately 86,000 per subdistrict; (2) assuming a crude birth rate of 17 per 1000 population per annum, 5% refuse, and 10% data losses, each subdistrict cluster would yield an average of 620 live births over 6 months; (3) an expected prevalence of stunting for children aged 0-23 months of 35% in the control clusters (based on unpublished survey data from Brebes, West Java, and Indonesian DHS data); (4) 80% power and 5% 2-sided alpha, and 1:1 ratio of interventions (subdistricts with and without the Baduta program) allocated; (5) design effect of 1.5 (lower than reported for the 2011 Indonesia DHS survey because of larger sized clusters); and (6) expected percentage point difference in the prevalence of stunting (0-23 months) between the intervention groups of 6% (35.0% in the control to 28.9% in the intervention group). (This is a relative reduction of 17%, which is lower than the 29% reduction in stunting reported in a recent meta-analysis [47] of education interventions to improve complementary feeding.)

A standard formula using established methods [48] for comparison of proportions to calculate the number of subjects required per intervention arm to test H_0: $\pi_0=\pi_1$ is as follows:

where $z_{\alpha/2}$ and z_{β} are standard normal distribution values for upper tail probabilities of $\alpha/2$ and β, respectively, π_0 is the proportion in control, π_1 is the expected proportion in intervention, m is the number of individuals per cluster, and ρ is the intracluster correlation coefficient.

Based on this calculation, the sample size required is 1392 mother-infant dyads from each group of 6 subdistrict clusters or approximately 232 mother-infant dyads per subdistrict cluster. We will round this up to 2800 mother-infant dyads per cross-sectional survey or 234 per subdistrict cluster. This sample size will provide 80% power assuming a Z score SD of 0.975 and 5% level of significance to detect a 0.15 Z score difference in height-for-age Z scores [49] between the intervention and the control groups in the end-line survey. Therefore, for the cross-sectional evaluation, we will select 2800 mothers of children aged 0-23 months and an additional 400 pregnant

women from 12 subdistricts within the Sidoarjo and Malang districts.

For the cohort evaluation, to detect a difference in mean length-for-age Z score between the experimental and control groups at an end line of 0.35 Z score [50], assuming 80% power and 5% level of significance, with a design effect of 1.5 (see above), we will require a sample size of 272 mother-infant pairs in each of the intervention and comparison groups. Assuming a dropout rate of 25%, we need to recruit 680 mother-infant pairs (56-57 per subdistrict cluster).

Sampling Procedure

In the cross-sectional evaluation, the sampling design will follow a 3-stage cluster sampling procedure. In the first stage, in each of the 12 subdistricts selected for the study, we will randomly select 10 villages using the probability proportionate to size sampling method. In the second stage, we will select 2 villages from each village using simple random sampling. In the third stage, in each of the selected subvillages, we will list all households and conduct a mini census of children aged <2 years and pregnant women. Using this framework, we will use simple random sampling to select 12 children aged <2 years and their mothers and 2 pregnant women.

In the cohort evaluation, we will construct a sampling frame of all pregnant women in their third trimester from all the selected villages using the client lists of midwives and health volunteers. We will systematically contact the pregnant women on the list across all 6 subdistricts to obtain the required sample.

Recruitment and Consent

We have described the approach and criteria for selecting clusters in the section above on *Cluster Selection and Design of Randomization*. We will seek *Gatekeeper* consent [26] from the heads of the 2 study districts, the selected subdistricts, and the sampled villages.

In both the cross-sectional and cohort evaluations, we will recruit either women with children aged <2 years or pregnant women from the village-level sampling frames by contacting them at home. Trained field staff will explain in detail the background and objectives of the study to the women and provide a written information sheet to all women contacted. Written informed consent was obtained from women who agreed to participate in the study.

Data Collection Methods

Data Collection Team

An organization not responsible for the intervention will recruit and manage a data collection team. For the cross-sectional evaluation, we will recruit 10 field coordinators, 130 interviewers, and 20 nurses or midwives to collect blood samples and to take anthropometric measurements. We will divide the staff into 10 field teams, with each team consisting of 1 field coordinator, 1 assistant field coordinator, 8 enumerators for interviews of mothers and caregivers of children aged <2 years, 2 interviewers for pregnant women, 1 interviewer for dietary data, and 2 anthropometry field workers who also collected the finger-prick blood sample for hemoglobin assessment using Hemocue. We will train the cross-sectional evaluation team for 1 week on an overview of the Baduta study, the use of the CommCare data capture app, household listing and data collection procedures, explanations of study instruments (listing forms and questionnaires), quality controls for data collection, and a field plan. The training will include a 1-day tryout to practice the household listing, interviews of mothers of children, and pregnant women using the CommCare data capture app.

For the cohort evaluation, we will recruit 2 field coordinators and 8 interviewers, all of whom will be graduates from a local nutrition academy. We will divide this staff into 2 field teams, 1 team for each district. We will train the cohort evaluation team for 1 week on an overview of the Baduta study, use of the CommCare data capture app, the schedule of cohort data collection, explanations of study instruments, anthropometry, dietary and hemoglobin assessment, and tryout of all the cohort data collection procedures. The 2-day training for blood collection will cover standard phlebotomy methods, use of Hemocue for hemoglobin assessment and its calibration, and a practice session in the field. The 2-day training for anthropometric measurements will be competency based and will use standardization procedures to check the performance (precision and accuracy) of the anthropometry field workers.

Data Collection Schedule

For the cross-sectional evaluation, we will conduct a household listing in each subcluster (hamlet) before the interviews to obtain a list of all children aged <2 years and pregnant women living in the subcluster. We will identify households by applying a sticker that has an identification number for each house listed. We will interview women at home but invite and accompany them and their selected children (aged <2 years) to a central location in the village to collect blood samples and record anthropometric measurements. We will use the same field methods for both the baseline and end-line surveys. We will conduct the end-line survey 2 years after the baseline survey.

For the cohort evaluation, the data collectors will visit each woman a total of 15 times from late in the third trimester of pregnancy until the child is 18 months old (Figure 3).

Types of Information Collected

For the cross-sectional evaluation, we will use the *house-listing form* (paper based) to record the identification number and collect household location and composition, including details about each member such as date of birth and gender. We will use a *registration module* (part of the CommCare app) to record the name and address of the potential respondents selected based on the house-listing form. This module will then direct interviewers to the appropriate questionnaire modules for children aged <2 years or pregnant women. The respondent will be either the mother and caregiver of the child aged <2 years or the pregnant women. The *questionnaires for children aged <2 years* (CommCare) will record the family sociodemographic characteristics, the history of pregnancy and delivery, the history of antenatal care services, exposure to the interventions (end line only), breastfeeding practices, use of integrated village health posts, morbidity, knowledge about breastfeeding,

self-efficacy for breastfeeding, socioeconomic status, food security, and use of mobile phones.

Similarly, the *questionnaires for pregnant women* (CommCare) will record family sociodemographic characteristics, the history of pregnancy and delivery, exposure to interventions, knowledge about breastfeeding, knowledge about food to eat during pregnancy, intention to breastfeeding, socioeconomic status, and food security. We will use a special-purpose module (CommCare) to record the *anthropometric and hemoglobin measurements*. We will capture *dietary intake data* from children aged <2 years and pregnant women using the multiple-pass 24-HR (paper-based).

For the cohort evaluation, in pregnancy and until the child is 18 months old, the field staff will collect information about the location and composition of the household, pregnancy knowledge, breastfeeding intention, infant feeding knowledge, household food security, birth outcome and delivery services, antenatal care, IYCF practices, utilization of integrated village health post services and immunizations, exposure to Baduta interventions, child morbidity, maternal and child dietary intake, maternal and child anthropometry, and hemoglobin assessment (Figure 3). We will capture *dietary intake data* from the children and pregnant women using the multiple-pass 24-HR (paper based for the women and electronic data capture for the children).

Digital Data Collection Tool

We will capture data electronically on Android tablets in the field using a special-purpose CommCare app developed for the study. The interviewers will record the information on structured, error-detecting forms on tablets or mobile devices and dispatch it directly to a server for cleaning and merging. The app will navigate the interviewers through the different questionnaires for women with a child aged <2 years or pregnant women or the different visit forms in the cohort evaluation. We will generate and distribute routine field team performance reports based on the data captured to help supervisors manage field activities.

Statistical Methods

The intention-to-treat principle will guide our data analysis, and we will include data from all participants even if they do not participate in all interventions. We will apply the guidelines of the Consolidated Standards of Reporting Trials statement for clustered randomized trials in the analysis and presentation of the results. We will conduct analyses at the woman or infant level adjusted for cluster randomization. Initially, we will assess the effectiveness of randomization by comparing potential confounding factors in both treatment groups. We will apply statistical tests with χ^2 tests for categorical variables and an adjusted Wald test or the Fisher exact test for continuous variables to assess for any significant difference between treatment groups. *P* values <.05 will be considered to indicate a statistically significant difference between the groups. For selected dietary analyses of continuous variables, we will use the nonparametric rank order statistic, Somers' D [51] (corresponding to rank-sum tests), as it can adjust for the cluster sampling design.

We will calculate frequency and percent distributions for categorical variables and mean and SD or median and interquartile range for continuous variables. We will characterize the dietary intake by age group, breastfeeding status (for infants aged 12-23 months), and intervention and comparison groups. We will generate medians and interquartile ranges for dietary intake distributions that are not normally distributed. We will plot the frequency distribution of IYCF practices by child age. We will also plot the frequency distribution of Z score indices (Z score curves) in 0.25 Z score intervals using a Lowes function to smooth the curves, and we will compare these distributions with the growth standard distribution. We will repeat these plots broken down by treatment groups.

For the cross-sectional evaluation, the primary analyses will compare the prevalence of stunting (low length-for-age<–2 Z score) and the 95% confidence intervals in each treatment group adjusted for clustering and any imbalanced baseline characteristics.

For the cohort evaluation, the models will include the treatment group as a fixed effect, the community cluster as a random effect to account for the cluster effect, and the impact of the interventions over time by testing for an interaction between time and intervention group. We will conduct analyses to identify the subgroups (eg, level of maternal education or household wealth categories) that modify the response to the intervention. We will check the model assumptions and make appropriate adjustments to the analysis where necessary. Secondary analyses will examine each outcome variable (length-for-age Z scores, feeding patterns, and mean nutrient intakes), taking into account the repeated measurements within children by using separate mixed models.

Linear mixed models will be used for continuous outcomes (eg, length-for-age Z scores), and generalized linear mixed models will be used for noncontinuous outcomes (eg, mixed logistic models for binary outcomes, such as, percentage exclusively breastfeeding). Models will include intervention or comparison groups as a fixed effect, infants as a random effect to account for repeated measurements, and community cluster as a random effect to account for cluster effects. We will use Stata V.15 (Stata Corp 2017; Stata Statistical Software: Release 15; Stata Corp LP) for all analyses.

Research Ethics

We obtained ethical approval for the study from the Faculty of Public Health, University of Indonesia (323/H2.F10/PPM.00.02/2016) and the Human Research Ethics Committee of the University of Sydney (Protocol number: 2015/115). Trained field staff carefully explained the background and objectives of the study to the women and gave a written information sheet to all women contacted. We obtained written informed consent from the women who agreed to participate in the study. We will maintain the privacy, anonymity, and confidentiality of the information provided by respondents during all phases of the study. We will store all information in an encrypted database with the participant's study identifier instead of personal identifiers, and only the investigators and authorized data management team will have access to the data collected.

Data Monitoring

On the basis of the CommCare data capture system, we will design a real-time study monitoring information system to provide information on enrolment status, adherence of the data collectors to the evaluation schedule, and the quality of key data elements. The system will generate automated emails to distribute information to field supervisors. Field supervisors will use this system to monitor the performance of individual data collectors, and all reports will be available for review by the investigators.

Data Access

All data collected will be accessible to the study investigators, who will have the right to analyze and publish data. We will make the relevant anonymized individual-level data available on reasonable request.

Results

Cross-Sectional Evaluation

We conducted the baseline survey for the cross-sectional evaluation in February 2015. We recruited 2435 mothers and their children aged <2 years, of whom 1199 were in the intervention group and 1236 were in the comparison group. Similarly, we recruited 409 pregnant women, of whom 198 were in the intervention group and 211 were in the comparison group.

We conducted the end-line survey in February 2017. We recruited 2740 mothers and their children aged <2 years, of whom 1357 were in the intervention group and 1383 were in the comparison group. Similarly, we recruited 642 pregnant women, of whom 306 were in the intervention group and 336 were in the comparison group.

Cohort Evaluation

We began recruitment to the cohort evaluation in February 2015 and completed the follow-up of participants in December 2016. We screened 729 pregnant women for their eligibility to join the study, of which 685 mothers (343 in the control group and 342 in the intervention group) who delivered their babies were followed up in the study till the child was 18 months old. Among them, 331 in the control group and 327 in the intervention group remained in the study until the end. There were 12 dropouts in the control group and 15 dropouts in the intervention group.

We completed data cleaning and processing for both evaluations in July 2017, followed by analysis, report writing, and dissemination of the results.

Discussion

Overview

Childhood undernutrition remains a global public health nutrition problem, with an estimated 150 million children worldwide with stunted linear growth, despite recent progress made to improve the nutritional status of children [52]. Although Indonesia is a middle-income country, it is ranked 25th globally for its prevalence of childhood stunting and fifth for the number of stunted children [53]. Furthermore, the prevalence of stunting among children aged <5 years in Indonesia between 2007 and 2013 has remained stagnant at 36%-37% [54]. The Government of Indonesia has established nutrition development targets and aims to reduce the prevalence of stunting among children aged <2 years from 33% in 2013 to 28% in 2019 [22]. Strong evidence is needed about effective intervention packages to reduce stunting to guide policy and program decisions at the national level and for the decentralized district governments. This paper describes a study protocol of a cluster randomized controlled study to assess the impact of a package of behavior change interventions and health system strengthening activities on maternal and child nutrition status.

Limitations

We designed the study to examine the impact of the package of Baduta nutritional and behavioral change interventions on the primary outcome, child stunting; therefore, we cannot identify the impact of the individual behavior change intervention components. We measured the exposure to the interventions in the end-line survey for the cross-sectional evaluation and at the end of the follow-up period at 18 months in the cohort evaluation. This information is for process evaluation, but we may use it to examine the associations between the individual intervention components and child growth in analytical epidemiological analyses.

The small number of clusters in which it was feasible to implement the interventions, especially the health systems interventions, prevented the use of simple randomization to allocate the treatments. We addressed this study design limitation through the use of restricted randomization [26,30] in which we used existing village census and health surveillance information to identify the set of combinations of the study subdistrict clusters that had a balance of characteristics or indicators that were related to the study outcomes. We randomly selected one of these balanced combinations to allocate study treatments.

A further limitation of the study is the lack of an economic analysis to assess the cost-benefit of the program for preventing child stunting.

Study Implications

In Indonesia, reaching the current nutrition targets for child stunting will require an integrated approach that includes support for appropriate IYCF practices, including exclusive breastfeeding for 6 months, continued breastfeeding for 2 years, timely and appropriate complementary feeding, improved maternal nutrition, access to quality health services, water and sanitation, and other public health measures. The results of this study will provide valuable inputs for future research on preventing child stunting and help to formulate and guide policies to support effective packages of nutrition behavior change interventions to prevent child stunting in Indonesia.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Map of Baduta impact evaluation districts in East Java.
[PNG File , 337 KB - resprot_v9i9e18521_app1.png]

Multimedia Appendix 2
Description of emo-demo sessions.
[DOCX File , 22 KB - resprot_v9i9e18521_app2.docx]

Multimedia Appendix 3
Emo-demo visuals.
[PNG File , 827 KB - resprot_v9i9e18521_app3.png]

Multimedia Appendix 4
Description of the four TV spots.
[DOCX File , 18 KB - resprot_v9i9e18521_app4.docx]

Multimedia Appendix 5
Baduta behaviour change messages in poster format.
[PNG File , 1189 KB - resprot_v9i9e18521_app5.png]

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Abbreviations

24-HR: 24-hour dietary recalls
DHS: Demographic and Health Survey

GAIN: Global Alliance for Improved Nutrition
Hb: hemoglobin
IYCF: infant and young child feeding
SEAMEO-RECFON: Regional Centre for Food and Nutrition, Southeast Asian Ministers of Education Organization
UNICEF: United Nations Children's Emergency Fund
WHO: World Health Organization

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Protocol

One-Way and Two-Way Mobile Phone Text Messages for Treatment Adherence Among Patients With HIV: Protocol for a Randomized Controlled Trial

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Abstract

Background: Incomplete adherence to antiretroviral therapy (ART) is one of the factors that contribute to HIV drug resistance, and it is a major problem for the public health system in controlling the HIV pandemic. There is emerging evidence that SMS can play an important role in health care delivery among patients with HIV on ART, especially in resource-limited settings.

Objective: This paper aims to assess the impact of two-way and one-way SMS text messaging on adherence to HIV treatment. We hypothesized that sending weekly text messages through the one-way and two-way SMS text messaging approach will improve adherence to ART among patients with HIV and improve associated clinical outcomes (quality of life).

Methods: A randomized controlled trial is being carried out among participants with HIV who have been on ART for at least one month from an accredited treatment center, namely the Buea Regional Hospital and Kumba District Hospital of South West Region, Cameroon. Participants with HIV, both male and female, aged 21 years and older make up a sample size of 207. The interventions involved the use of mobile phone text messages. Before commencing the intervention, a focus group discussion was carried out among the participants to understand their perception about the use of SMS-based interventions to improve adherence. A total of 246 participants were randomized to receive either a one-way text message (SMS sent to a recipient without recipient sending a reply) or two-way text message (SMS sent to a recipient and recipient sends a reply) or the control (no SMS, only standard care). Data on adherence and quality of life were collected at baseline and after 6 months and will be analyzed using SPSS version 21, while qualitative data will be analyzed using Atlas.ti 7.5.

Results: Data collection began in September 2019 with focus group discussions and baseline data collection. After 1 month of baseline data collection, the intervention began in October 2019, and postintervention data were collected after 6 months (March 2020). At the end of the study, we will be able to understand the perception of patients toward SMS text messaging–based interventions and also assess the impact of one-way and two-way SMS text messages on treatment adherence among patients with HIV and on associated clinical outcomes (quality of life).

Conclusions: The impact of SMS text messaging varies across different settings. The results from this study will determine the perception of patients toward an SMS text messaging–based intervention and its impact on adherence to ART.

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KEYWORDS

HIV; antiretroviral therapy; short message service; adherence

Introduction

Medication adherence is defined by the World Health Organization as the degree to which a person's behavior corresponds with the agreed recommendations from a health care provider or as the extent to which the patient's history of therapeutic drug taking coincides with the prescribed treatment. The Joint United Nations Programme for HIV and AIDS (UNAIDS) has defined new ambitious targets that call for 90% of people living with HIV to know their status, 90% of those diagnosed to receive antiretroviral therapy (ART), and 90% of those on treatment to achieve an undetectable viral load. This is known as the 90-90-90 target [1]. In 2018, 37.9 million people were living with HIV worldwide [2]. Scale-up of antiretroviral therapy is on a fast-track trajectory that has surpassed expectations. The global coverage of antiretroviral therapy reached 46% (43%-50%) at the end of 2015 [1]. In sub-Saharan Africa, where the majority of people receiving antiretroviral therapy live, timely access to HIV diagnosis and linkage to care remain the main challenges to achieving the 90-90-90 objective. In 2018 in Cameroon, 74% of people living with HIV knew their status, and only 52% of people living with HIV were on treatment [2].

Incomplete adherence to antiretroviral therapy is one of the factors that contribute to HIV drug resistance, HIV disease progression, and death [3,4]. Most patients do not adhere to ART due to the long duration of HIV treatment (lifelong therapy) and associated side effects [5]. Diverse strategies have been tested and implemented to help improve adherence to ART.

There is emerging evidence that mobile phones can play an important role in health care delivery, especially in resource-limited settings [6]. The use of phones to promote adherence has grown as phone ownership rates continue to rise in sub-Saharan Africa and elsewhere [7,8]. SMS text messaging is a particularly useful application that can be used to collect or share information and to enhance communication between health care personnel and patients in a low-cost manner [9]. With regard to patient management, mobile phone text messages have been demonstrated to induce positive behavior changes in domains such as smoking cessation, physical activity, and self-management of high blood pressure, diabetes, and asthma [10]. Other studies report high levels of satisfaction among participants [11,12]. Considering these studies, it is possible to conclude that SMS is effective in inducing a positive behavior change and providing greater connectedness with a provider.

Some studies have shown the effectiveness of SMS in improving adherence. For example, a recent Cochrane systematic review synthesizing data from 2 trials conducted in Kenya by Lester and colleagues [12] showed that text messaging is efficacious in improving adherence. They tested a two-way SMS intervention in which recipients in the intervention group were required to respond to weekly messages inquiring about their well-being within 48 hours, with those indicating that they did not feel well or not responding at all receiving outreach from clinic staff. They found a 12 percentage point increase in the likelihood of self-reported adherence greater than 95% among HIV-positive adults in 3 clinics, as well as a 9 percentage point increase in rates of viral suppression. The use of SMS text messaging was also shown to be effective by Pop-Eleches and colleagues [13]. They reported a 13 percentage point increase in the likelihood of achieving at least 90% electronically monitored adherence over 48 weeks in the intervention group that received one-way weekly SMS messages. In another study, Hailey and Arscott [14] showed a significant increase in adherence rates (40% to 50% at baseline to 80% after 24 months) among youths living with HIV after sending a text message reminder and receiving a reply over a 24-month period. However, the youths did not send text messages about their drug refills, shortages of their medications, and adverse effects of the medications they were receiving. Due to the fact that this intervention prevented the patients from sending text messages about adverse effects and the state of their well-being, it is possible to question their quality of life and its impact on adherence. Though SMS text messaging can increase adherence rate, poor quality of life can affect adherence if the content of the text does not address issues related to quality of life.

A study carried out in Cameroon reported a contrary view on SMS text messaging improving adherence [15]. In addition, another study carried out by Linnemayr and colleagues [16] also reported the ineffectiveness of SMS text messaging in improving adherence.

However, despite the quality of evidence generated from literature [10-14] on the importance of SMS-based interventions in improving adherence treatment, especially ART, it remains unclear if the efficacies observed in this existing literature translate into effectiveness in different settings. The fact that a text messaging intervention is effective in a particular setting does not signify its effectiveness in other settings. Some text message–based interventions are ineffective because researchers did not understand or take into consideration the conditions under which the SMS text messaging intervention should be implemented and the content of the message. It is also important to find out what aspect of behavior change the text messaging affects and how it can generally cause behavior change. The findings from this study will be used by health care providers to effectively design an SMS text messaging intervention that is applicable to the setting and the target population.

The general objective of this study will be to assess the impact of the interventions (two-way and one-way SMS) on adherence to ART. We hypothesize that sending weekly text messages through the one-way and two-way SMS text messaging approach will improve adherence to ART among patients with HIV and improve associated outcomes (quality of life).

Methods

Study Setting and Participants

The participants were selected from accredited treatment centers, namely the Buea Regional Hospital and Kumba District Hospital of South West Region, Cameroon. Participants included adults (male and female) aged 21 years and older who were infected with HIV and visiting the health centers for routine health education and drug refill appointments. The study recruited

participants that were on highly active antiretroviral therapy (HAART) for at least 1 month and who had mobile phones and were able to read and send text messages. We excluded pregnant women and patients with drug-resistant HIV prior to the commencement of the study.

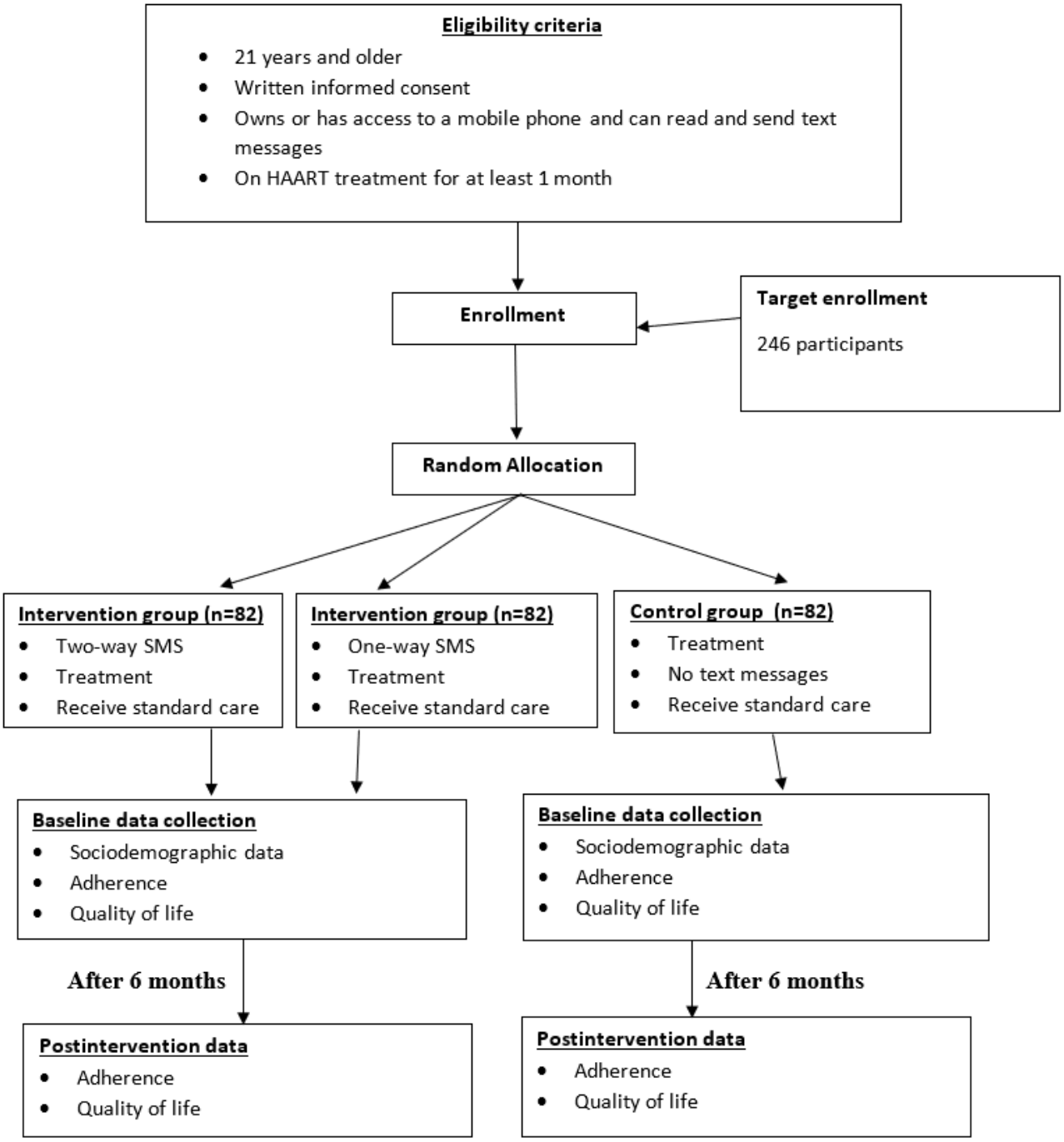
Study Design

A qualitative study design involving the use of focus group discussions (FGDs) was used to assess the perception of patients on the use of SMS text messaging–based intervention. Thereafter, a quantitative study design involving a randomized controlled trial was carried out. The intervention used one-way or two-way SMS text messaging. Adherence and quality of life (QoL) were measured at baseline and at postintervention in control and intervention groups. Adherence in the control group will be compared with the adherence in the intervention groups before and after the intervention. Likewise, the QoL in the control group will be compared with the QoL in the intervention groups before and after the intervention. In addition, the impact of adherence on QoL will be assessed in the control group and intervention groups before and after the intervention.

Intervention

The interventions involved the use of mobile phone text messages in addition to the standard care provided to the participants. Participants were randomized into either a one-way text message group (text message sent without receiving a reply) or two-way text message group (text message sent to recipients and the recipient replies to the SMS sent). Text messages were sent both in English and in French, and airtime was purchased from the mobile telephone network. In the morning periods, messages were sent 3 times a week (Mondays, Wednesdays, and Fridays between 8 AM and 10 AM) from an established list of phone numbers of the participants during the study period. The control group received only the standard care given at the hospital. The random allocation of participants in the intervention and control group is shown in Figure 1. The intervention used in this study is based on the nudge theory, which is an approach to understanding and changing people's behavior by analyzing, improving, designing, and offering free choices for people so that their decisions are more likely to produce helpful outcomes for those people and society generally. The SMS text messaging acts as a nudge in order to influence a positive behavior change, which is adherence to ART.

Figure 1. Flow diagram on the randomization of participants into the intervention and control groups. HAART: highly active antiretroviral therapy.



Study Duration

This study will be carried out over a period of 1 year. The intervention phase ran for 6 months after collecting baseline data (preintervention data) on adherence and quality of life.

Sample Size

The formula by Chan [17] for calculating the sample size for randomized controlled trials was used:

In the above equation, $c = 7.9$ for 80% power and $p1$ and $p2$ are the proportion estimates (60% for the control group and 82% for the intervention group).

n (size per group) = 63.27 **(3)**

It was assumed that 30% of the participants would drop out of the study due to loss to follow-up and mortality. A total of 82 participants were then randomized to each group to allow for the 30% drop out (30% of 63 participants = 19). In order to make up for the 19 that was assumed to be lost to follow-up, we added the 19 participants to the calculated 63 participants, giving a total of 82 participants. Therefore, a minimum of 246 participants were recruited into the study.

The above sample size in each group was distributed with 164 in the intervention group (82 in the two-way SMS group and 82 in the one-way SMS group) and 82 in the control group.

Evaluation of Intervention

A logbook was used to register all SMS text messages sent and replies received on the designated days of the week. A delivery report function was used to ensure that the messages were delivered to the participants. The sent text and responses received will be evaluated by calculating the proportion of SMS text messages sent and responses received. Example text messages are shown in Textbox 1.

Textbox 1. Examples of the text messages that were sent.

- "Hello. Do remember to take your medication as prescribed. Your health is your wealth."
- "You are kindly reminded to take your medication. Your health is our priority."
- "Don't forget to take your medications."

Randomization

Using a simple randomization technique, participants were recruited into the intervention and control group. Allocation of the participants into the groups (intervention or control) was concealed during the randomization procedure. This shall be a double-blind controlled trial: data collectors and the statistician shall be blinded to the different group allocations.

Data Collection Tools

A pretested structured questionnaire was used to obtain information from the participants on sociodemographic characteristics, adherence to treatment, quality of life, and past health history. A logbook was used to report on all messages that were sent during the week and the number of replies received, and the research team recorded all defaulters and participants lost to follow-up.

Measurement of Adherence

The overall adherence of each participant was measured using 2 scales of self-report, namely the visual analog scale (VAS) [18] and the Center for Adherence Support Evaluation (CASE) Adherence Index [19]. VAS appears to be a simple and easy to use measure of adherence, though there is mixed literature about this. VAS has been shown to have large strength associations with most other measures of adherence. A 100-point VAS will be used, with 0 indicating "absolute nonadherence" and 100 indicating "excellent adherence" in the last 30 days. A VAS score equating to at least 95% will be defined as optimal adherence and VAS scores less than 95% will be considered suboptimal.

The CASE Adherence Index is a simple composite measure of self-reported ART adherence. Based on the results of correlation and principal components analyses, the CASE Adherence Index is developed as a composite (sum) of 3 self-reported measures of adherence. The CASE Adherence Index can be seen in Multimedia Appendix 1.

Measurement of Quality of Life

The quality of life was assessed using the abbreviated World Health Organization Quality of Life (WHOQOL-BREF). This is an international, cross-culturally comparable quality of life assessment instrument. It assesses the individual's perceptions in the context of their culture and value systems and their personal goals, standards, and concerns. The WHOQOL-BREF instrument comprises 26 items, which measure the following broad domains: physical health, psychological health, social relationships, and environment [20]. The quality of life among the participants with HIV was assessed using the WHOQOL-HIV BREF. The WHOQOL-HIV BREF is based on the WHOQOL-BREF, the shorter form of the WHOQOL-100. This contains 5 extra items specific to people living with HIV/AIDS and in total contains 31 items [21].

Focus Group Discussion

A FGD discussion guide was pretested and fine-tuned before implementing it in the study. A total of 8 FGDs will be organized under 4 main themes: (1) predictors of nonadherence to ART, (2) awareness of the use of mobile health (SMS) to improve adherence to ART, (3) content of the text that will be acceptable for use to improve adherence to ART, (4) choice of approach to text messaging services (one-way or two-way), and (5) possible challenges in the implementation of mobile health (via SMS). All FGD sessions will last for 50 to 60 minutes and be moderated by a moderator. At the end of the study, a FGD will be conducted to discuss the challenges the participants faced with respect to text message reminders and replies.

Study Outcome

Primary Outcome

The primary outcome is to assess the impact of the one- and two-way SMS text messages on treatment adherence among patients with HIV. Measures of adherence from the CASE Adherence Index and the VAS will be used to measure the overall adherence.

Secondary Outcome

The secondary outcome is to assess the impact of the intervention on quality of life and the impact of quality of life on adherence.

Data Management and Statistical Analysis

Data from the questionnaires will be checked each time they are brought from the field for unfilled and unanswered questions, including the verification of codes. All verified data and codes will be keyed into Microsoft Excel and research questionnaires will be kept in a secured locker. The analysis of patient demographics and study outcome variables will be summarized using descriptive summary measures, expressed as mean (standard deviation) or median (minimum-maximum) for

continuous variables and number (percentages) for categorical variables. A 1-tailed *t* test shall be used for comparing groups on continuous outcomes, and the chi-square test will be used for binary outcomes, as shown in Table 1. Analysis of variance will be used to analyze the statistical differences among more than two group means. All statistical tests will be performed using 2-sided tests at the .05 level of significance. All statistical analyses will be performed using SPSS (version 21.0; IBM Corp).

Table 1. Statistical tests to be used for different variables.

Outcome variables	Scale	Type	Measure	Analysis method
Primary				
Adherence at baseline and at 6 months				
CASE[a] Adherence Index	Ordinal	Binary	Adherence in last month ≥95%	Chi-square test
VAS[b]	Ordinal	Binary	VAS percentage ≥95%	Chi-square test
Secondary				
Quality of life	Ordinal	Categorical	Change in QoL[c] scores	*t* test ANOVA[d]

[a]CASE: Center for Adherence Support Evaluation.

[b]VAS: visual analog scale.

[c]QoL: quality of life.

[d]ANOVA: analysis of variance.

Ethical Considerations

Ethical approval for this study has been obtained (No. 2018/764-03/UB/SG/IRB/FHS) from the Faculty of Health Sciences Institutional Review Board of the University of Buea, including an administrative authorization from the South West Regional Delegation of Public Health, Cameroon. In this study, patients have voluntarily confirmed their participation in the study. They were enrolled in the study upon receipt of signed informed consent from the participant. Names and national identity card numbers shall not be used to identify the participants, but rather, codes shall be used. This will keep the participants anonymous. Secondly, in order to prevent social stigma, the mobile phone text message reminders will not disclose a participant's seropositive status.

Results

Data collection began in September 2019 with focus group discussions and baseline data collection. After 1 month of baseline data collection, the intervention began in October 2019 and postintervention data were collected after 6 months (March 2020). At the end of the study, we will be able to assess the perception of patients toward SMS-based interventions and also assess the impact of the one- and two-way text messaging on treatment adherence among participants with HIV and on associated outcomes (quality of life). At baseline, the adherence and QoL in the control group will be compared with adherence and QoL in the intervention group, as well as at postintervention. Thus, the baseline results will be compared with the postintervention data to determine the impact of the intervention on adherence and on QoL. Adherence will be compared with QoL across all the groups at baseline and at postintervention.

Discussion

Overview

Despite the incredible success of the large-scale public sector provision of ART to HIV-infected people, failure to retain these patients on long-term treatment threatens to undermine the massive gains made since 2004 and remains one of the most critical obstacles to achieving the UNAIDS 90-90-90 targets for 2020, which are a key milestone toward ending the HIV epidemic by 2030 [22]. Diverse strategies or interventions have been put in place to improve adherence to ART. Research has shown that very high levels of adherence are required to obtain the maximum benefit of HAART. This situation justifies the importance of developing efficient strategies to improve adherence to ART [23].

There is emerging evidence that mobile phones can play an important role in health care delivery, especially in resource-limited settings [6]. The appeal of using phones to promote adherence has grown as phone ownership rates continue to rise in sub-Saharan Africa and elsewhere [8]. SMS text messaging is a particularly useful application that can be used to collect or share information and to enhance communication between health personnel and patients in a low-cost manner [9]. With regard to patient management, mobile phone text messages have been demonstrated to induce positive behavior changes in domains such as smoking cessation, physical activity, and self-management of high blood pressure, diabetes, and asthma [10]. Other studies report high levels of satisfaction among participants [11,12]. With Africa currently undergoing a digital revolution, the World Health Organization Regional Office for Africa and the International Telecommunication Union signed a cooperation agreement in Geneva on October 26, 2017, the focus of which was on how best to use digital services to save lives and improve people’s health [24].

The intervention in this study uses the health belief model of behavior change [25]. The data on the perceived barriers to adherence will be collected (through FGDs) and, as a cue to action for patients to adhere to treatment, the efficacy of text message reminders will be tested.

Conclusion

The impact of SMS text messaging varies across different settings. The results from this study will determine the perception of patients toward text message–based interventions and the impact of text messaging interventions on health care delivery among patients with HIV on ART.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The CASE Adherence Index.
[DOCX File , 13 KB - resprot_v9i9e16127_app1.docx]

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Abbreviations

ART: antiretroviral therapy
CASE: Center for Adherence Support Evaluation
FGD: focus group discussions
HAART: highly active antiretroviral therapy
QoL: quality of life
UNAIDS: Joint United Nations Programme for HIV and AIDS
VAS: visual analog scale
WHOQOL-BREF: abbreviated World Health Organization Quality of Life

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Protocol

A Mobile Gaming Intervention for Persons on Pre-Exposure Prophylaxis: Protocol for Intervention Development and Randomized Controlled Trial

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Abstract

Background: In the United States, young minority men who have sex with men (MSM) are the most likely to become infected with HIV. Pre-exposure prophylaxis (PrEP) is an efficacious and promising prevention strategy. However, PrEP's safety and effectiveness can be greatly compromised by suboptimal adherence to treatment. To maximize the positive impact of PrEP, it is necessary to combine its prescription with cost-effective behavioral interventions that promote adherence and decrease HIV risk behaviors. In this project, we developed a theoretically informed app/gaming intervention to engage young MSM in learning information, practicing behaviors, and improving motivation for HIV preventative behaviors and PrEP adherence.

Objective: The goal of this project was to develop and test a cutting-edge, engaging, and entertaining app/gaming intervention for improving adherence to PrEP and building HIV prevention knowledge, skills, and behavior.

Methods: This study was conducted in two phases. In the developmental phase, we conducted qualitative interviews with young MSM (n=20) to guide the development of the gaming intervention. In the randomized controlled trial, we tested the preliminary efficacy of the gaming intervention compared to a comparison condition among young MSM. Subjects were recruited from the University of Mississippi Medical Center HIV/STI testing clinics (n=60).

Results: Institutional review board approval was received in February 2015. Research activities began in June 2015 and are still ongoing.

Conclusions: This app/gaming intervention aimed to improve PrEP adherence and HIV preventative behaviors in young MSM. Engaging young MSM in learning information, practicing behaviors, and improving motivation for increased adherence to PrEP has the potential to decrease HIV seroconversion. It is important to develop interventions that are enjoyable, engaging, and easily incorporated into clinical settings.

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KEYWORDS

pre-exposure prophylaxis (PrEP); adherence; mobile gaming intervention; HIV prevention; men who have sex with men (MSM)

Introduction

Background

The primary prevention of HIV infection remains a crucial priority. In 2011, there were 2.5 million new HIV infections worldwide [1]. In the United States, young minority men who have sex with men (MSM) are the most likely to become infected with HIV. Antiretroviral (ARV) medications that reduce the risk of acquiring HIV infection, namely pre-exposure prophylaxis (PrEP), are an efficacious and promising prevention strategy [1,2]. There have been significant advances regarding PrEP including the definitive demonstration that PrEP reduces HIV acquisition, regulatory approval of Truvada (tenofovir/emtricitabine or TDF/FTC) with an indication for sexual HIV prevention, and development of clinical prescribing guidelines. Despite these promising events, the practical implementation of PrEP is challenging [3-10]. Data show that PrEP's safety and effectiveness could be greatly compromised by suboptimal adherence to treatment, and there is concern about the potential for an increase in HIV risk behavior among PrEP users [11-15]. Due to these challenges, the prescribing of PrEP should be accompanied by behavioral interventions.

Supporting the idea that adherence to medical care is an integral factor in PrEP's effectiveness, the iPrEx, TDF2, and Partners PrEP clinical trials all conclusively showed that the level of protection from HIV infection depended on how consistently participants took prescribed medication [16-18]. Significantly greater levels of protection occurred among participants with detectable levels of ARVs in these trials. The impact of adherence was also underscored in the FEM-PrEP and VOICE studies, both of which found that few women had detectable levels of ARVs; thus, the studies were unable to demonstrate the efficacy of PrEP [15,19,20]. In 2013, the nested substudy of the Partners trial found that high (>80%) PrEP adherence was associated with 100% efficacy (95% CI 83.7%-100%) [17]. It is clear that the success of PrEP interventions highly depends on good adherence [14-17]. However, concerningly low rates of adherence to PrEP are seen in diverse samples of young Black MSM at high risk of acquiring HIV. Among a sample of 178 young MSM on PrEP (86% identified as Black/African American; median age 26 years; from North Carolina, Washington DC, and California), 36% did not meet the laboratory sensitivity threshold for ≥4 doses/week as measured by FTC/TDF levels in plasma and peripheral blood mononuclear cells at 26 weeks after PrEP initiation [21].

Adherence to PrEP medication is critical; however, engaging patients in comprehensive follow-up care is also imperative [22]. Treatment with PrEP requires consistent contact between patients and clinical providers and includes appointments with clinicians every 3 months for laboratory monitoring, HIV testing, and the detection and treatment of associated side effects [5,9,11-15]. Individuals who are at highest risk of HIV infection often come from populations that historically have been underserved by the health care system [23,24]. Therefore, engaging patients in care could be challenging and will require reinforcement and support for doctors and patients [13,23]. Consequently, behavioral interventions that promote adherence to comprehensive PrEP treatment will need to be tailored to underserved and at-risk populations and will need to reinforce the clinician-patient relationship.

Although there is great optimism about the use of PrEP for HIV prevention, there is concern that PrEP users may take more sexual risks or underutilize traditional risk reduction strategies, such as condom use and HIV and sexually transmitted infection (STI) testing of partners. Behavioral models (behavioral disinhibition and risk compensation) suggest that risk could increase with the reduction of self-imposed constraints or by decreasing individuals' perceptions of HIV risk. This, in turn, could lead to increased incidence of HIV and other STIs [14,25-28]. Some mathematical and cost-effectiveness models have suggested that even small increases in risk behavior could offset or reverse PrEP's protective benefits at the population level [13,14]. Data from the iPREX study showed only indirect evidence of increased risk behaviors, as those participants who engaged in unprotected anal sex were more likely to have detectable tenofovir levels than those with less sexual risk taking [17,29]. In real-world clinical settings in which people know that they are actively on a prophylactic medication, behavioral risk taking could measurably increase. Increases in risk behaviors have been documented in the context of microbicide trials, in vaccine trials, and among patients living with HIV on ARV therapy (ART) [30]. Therefore, HIV prevention counseling remains clinically relevant and prudent when prescribing PrEP. This practice is consistent with good clinical care and is recommended in interim guidelines for prescribing PrEP, which state that PrEP has the potential to contribute to effective and safe HIV prevention for MSM if "it is delivered as part of a comprehensive set of prevention services, including risk-reduction and PrEP medication adherence counseling" [22]. Therefore, in order to maximize the positive impact of PrEP, it is necessary to combine the prescription of PrEP with behavioral interventions that promote both adherence and the reduction of HIV risk behaviors [2]. However, these accompanying behavioral interventions need to be cost-effective and easily integrated into clinical settings in which PrEP is prescribed [15]. Additionally, interventions should be enjoyable and tailored to populations targeted for prevention with PrEP. Without these necessary components, integration of behavioral interventions into clinical settings cannot be realistically sustained.

There are many advantages to using newer interactive technology and gaming to promote adherence, rather than traditional face-to-face counseling, including scalability, efficiency, and cost-effectiveness. The use of an intervention that utilizes gaming technology is particularly compelling for use with younger adults who are heavy utilizers of mobile technology and who are most at risk for acquiring HIV. Games can attract and maintain attention, which is a key component for effective behavior change. Compelling, interactive, phone-based games can expose players to essential health-related content countless times and give players unlimited opportunities to rehearse new skills and receive personalized feedback on health choices made within the game [31-33]. Games have been shown to be efficacious in promoting fitness, improving weight management, and improving safer sex skills [31,33-35]. For example, a HIV/AIDS-prevention computer game called *Life*

Challenge was developed by the New York State Department of Health to enhance safer sex negotiation by adolescents and young adults. The game showed significant improvement in self-efficacy for partner negotiation and condom skills for those who started with the least self-efficacy [33]. Two pregnancy prevention games, *The Baby Game* and *Romance*, designed for sexually active young adults showed trends in improving knowledge and attitudes about parenting and unprotected sexual behaviors [32].

Video games have also been applied to improve self-management skills and healthy behaviors in those living with asthma, diabetes, and cancer [36-40]. A video game named *Re-Mission*, designed for a wide age range of patients, namely 13-29 years old, with acute leukemia, lymphoma, and soft-tissue sarcoma, showed promising effects as well. *Re-Mission* was designed as an action-adventure game with the main character or protagonist shooting cancer-causing agents in the bloodstream. Players gained points and strength by adhering to medications in the game fantasy world. In a randomized control trial (RCT) with a 3-month follow-up, 375 male and female participants who played *Re-Mission* had significantly improved adherence to trimethoprim-sulfamethoxazole (*P*=.012) and 6-mercaptopurine (*P*=.002) compared to controls after an average of only 10.7 hours of play. Adherence to trimethoprim-sulfamethoxazole was tracked by electronic pill monitoring devices (n=200). The proportion of doses taken correctly by those playing *Re-Mission* was 19% greater than those in the control group. Self-efficacy (*P*=.011) and knowledge (*P*=.035) also increased significantly compared with the control group. Interestingly, the intervention did not affect subjective self-report measures of adherence but did affect the aforementioned objective measures [39,40]. Thus, appealing interactive games can target information, motivation, and skills for medical care and lead to a broad spectrum of desirable outcomes including increases in knowledge, attitude changes, and increased medication adherence [34,35,41-43].

Very few studies describe outcomes of theory-driven PrEP adherence interventions, and there are no other publications on gaming interventions to improve PrEP adherence. Fuchs et al [44] showed that a mobile health intervention using weekly bidirectional messaging (iText) was acceptable and demonstrated promising effects on PrEP adherence in a within-subjects trial design. This sample included MSM from San Francisco and Chicago (one-quarter were under 30 years of age, 13% were Black/African American, 11% were Latino, and 88% completed some college). A pre-post intervention regression discontinuity analysis using clinic-based pill counts showed a 50% reduction in missed doses (95% CI 16%-71%; *P*=.008) and a 77% improvement (95% CI 33%-92%; *P*=.007) when comparing pill counts at quarterly visits before and after iText enrollment. Liu et al [45] reported on the outcome of PrEPmate, a bidirectional text-messaging intervention, on study visit completion and tenofovir diphosphate (TFV-DP) concentrations assessed at 4, 12, 24, and 36 weeks among 121 participants (mean age 24 years; 27% Black, 36% Latino) living in Chicago. Participants who received PrEPmate were more likely to attend study visits (86% PrEPmate vs. 71% non-PrEPmate, OR 2.62, 95% CI 1.24-5.54) and have TFV-DP levels consistent with ≥4 doses/week (72% PrEPmate vs. 57% non-PrEPmate, OR 2.05, 95% CI 1.06–3.94). Although these studies showed promising preliminary effects and feasibility, there are no known definitive, scalable, evidence-based gaming interventions to improve adherence to PrEP.

Theoretical Framework for Intervention

The Information-Motivation-Behavioral Skills (IMB) model is a well-established conceptualization for improving adherence to treatment as well as decreasing HIV risk behaviors. HIV prevention and ART adherence interventions based on IMB have demonstrated efficacy [46-48], and reviews have suggested that interventions guided by accepted theories of change are more efficacious than those not driven by theory [49]. According to the IMB model, health information, motivation, and behavioral skills are the fundamental determinants of health behavior. In order for a PrEP-related intervention to be successful, the PrEP user must learn information that is directly relevant to PrEP adherence and HIV transmission. Knowledge is a necessary but not sufficient condition for change. Personal motivation to engage in HIV preventative behavior or adhere to treatment regimens (attitudes about health) and social motivation (perceived social and cultural support for performing these acts) are essential for change. Finally, skills for performing adherence behaviors and a sense of self-efficacy must be easily applied to an individual's cultural and social setting. The most recent review of factors associated with PrEP adherence suggests that adherence can be facilitated by "accurate knowledge of medication benefits," "medication optimism and self-efficacy for adherence," and "support provided by peers and providers" [50]. Our intervention addresses these factors within the context of the IMB model. This model, consistent with Social Learning Theory, is broadly applicable and can be used to create theoretically consistent intervention content [51].

Aims and Objectives

The aims of this project were to develop and test a cutting-edge, engaging, and entertaining app/gaming intervention to improve adherence to PrEP and build HIV prevention knowledge, skills, and behavior. The effectiveness of a novel, scalable, technology driven intervention to improve PrEP adherence is understudied. Consequently, through this RCT, we aimed to leverage technology to engage patients in learning skills, practicing behaviors, and improving motivation for adherence and healthy behaviors. We are not aware of any PrEP-related intervention that utilizes a theoretically informed game. An engaging, technology-based intervention may empower and engage PrEP users, aid over-burdened clinics, and result in improvements in health.

Methods

Trial Registration and Institutional Review Board Approval

This research involving human subjects took place at collaborating sites. The protocol was reviewed by the Institutional Review Boards of Brown University, Lifespan/Miriam/Rhode Island Hospital (RIH), and the University of

Mississippi Medical Center (UMMC). This study is also registered on ClinicalTrails.gov (RCT02611362).

Design

This research was divided into two major phases. First, a developmental phase (n=20, 18-35 years old, receiving PrEP) consisted of formative research to guide the development of the app/gaming intervention. Second, in an RCT phase, we evaluated the preliminary efficacy of the PrEP-related IMB app/gaming intervention compared to a comparison condition — a non-PrEP–related, non-IMB–informed game (n=60, 18-35 years old, receiving PrEP). Subjects were recruited from and consented in person at the UMMC.

Participants

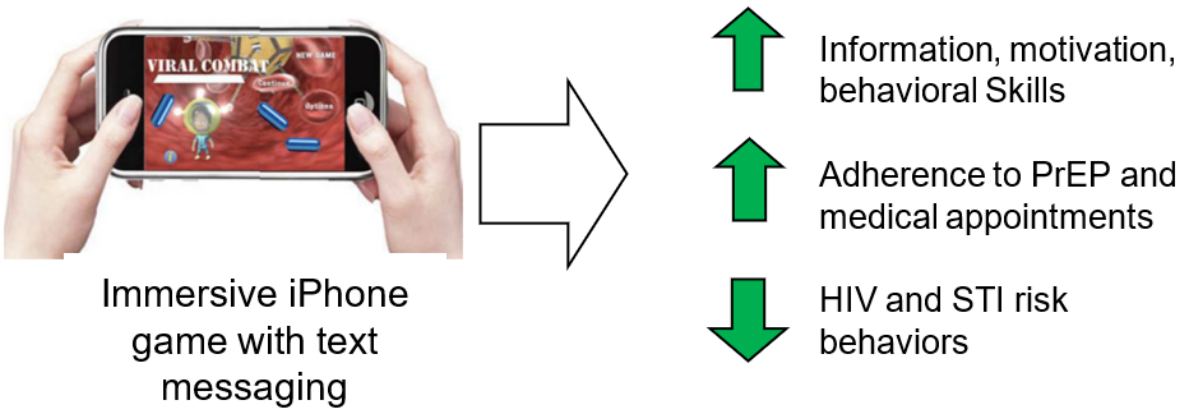
All MSM initiating PrEP between the ages of 18 and 35 years were eligible for enrollment in each phase of study according to the following criteria: (1) English speaking, (2) initiating PrEP, (3) not enrolled in another PrEP-related study, (4) able to give consent or assent, and (5) not impaired by cognitive or medical limitations as per clinical assessment. Clinical assessment occurred by members of the research team with substantial prior clinical (medical and psychiatric) and research experience in care of young adults and adults. There was no overlap between subjects in the developmental and RCT phases. We enrolled only MSM because they are the group most at risk for acquiring HIV. Limiting the study to MSM allowed for the development of an iPhone app/game that was targeted, acceptable, and engaging for this specific at-risk population. Based on previously acquired data, it was estimated that 65% of participants would be Black/African American, 30% would be Hispanic, and the mean age would be 27 years. A total of 20 participants were recruited for the developmental phase and 60 for the RCT phase over a period of 24 months.

Description of Intervention Content

The gaming intervention developed for this project by Mission Critical Studios was titled *Viral Combat.Viral Combat* was consistent with the IMB Model of Health [52] and promoted increased self-efficacy for adherence to PrEP and HIV preventative behaviors by improving motivation and knowledge about health and prevention and by increasing mastery of skills. Successful games are intuitive, engaging, and inherently rewarding through action and feedback. Many of the attributes of a successful game are a natural fit for a successful IMB-informed intervention.

Participants playing *Viral Combat* fight off HIV and keep it from entering a virtual body. The game takes place on the surface of the skin, in the arterial system, and in the penile and anal canals. HIV-related educational material (eg, puzzles and quizzes) were tailored to prevent HIV (ie, importance of testing and using condoms) and not tailored to persons living with HIV (ie, how viral load affects transmission and health). Adherence messages were relevant to participants using PrEP for HIV prevention (ie, taking PrEP doses as prescribed corresponds to the level of protection). *Viral Combat* employs graphics, characters, and action content specifically chosen to appeal to our target population. All organ systems are vibrant and distinctive. Answering questions from the doctor or clinician and building adherence and HIV prevention knowledge allows each player to earn strength and points throughout *Viral Combat*. During play, if an answer to a question or skill-building exercise is wrong, the player is alerted, and the correct answer is explained. “Health Facts” reinforce HIV prevention information during scene changes. HIV prevention skills are built with a condom “puzzle” and the “condom use challenge” that promotes continued condom use with all partners. Each level in *Viral Combat* provides new challenges and unique and colorful environments. However, the mission stays the same: Kill the virus and build strength through taking medicine, learn HIV prevention information, improve motivation, and engage with healthy charcters in order to build skills. All character controls and gaming are achieved using touch screen technology on the phone with no additional accessories needed. Throughout the game, the terms “HIV,” “AIDS,” “antiretroviral,” and other identifying verbiage are avoided to protect the players’ medical status and to avoid possible stigmatization that could occur from someone seeing a participant playing the game (See Figure 1).

Figure 1. Goals and components of the multilevel gaming intervention. PrEP: pre-exposure prophylaxis; STI: sexually transmitted infection.



Developmental Phase

Overview

The goal of the developmental phase (n=20) was to develop and refine the game *Viral Combat* for the intervention. This phase established acceptability and feasibility of the gaming intervention by participants. These steps were accomplished with preliminary work by the scientific investigators in collaboration with Mission Critical Studios. Multiple reviews have demonstrated that behavioral interventions shown to be most efficacious are tailored for the target population and preceded by formative research to inform intervention development [53-55]. During the developmental stage, we elicited feedback from participants regarding the gaming intervention. Necessary changes were made if participants felt the game content or title was revealing, insensitive, or stigmatizing.

Individual Qualitative Interviews

In-depth, structured individual interviews about the utility and appeal of the gaming intervention were conducted with approximately 20 participants during the development phase. Interviews continued until redundancy in major themes occurred. We ensured that the assembled intervention was oriented to the appropriate ages, genders, and sexual orientations of participants and that it was relevant and consistent for our target population. Enrollment was monitored to ensure that there was adequate representation of gender, ethnic, racial, sexual orientation, and age diversity among participants. An overview of the IMB Gaming Adherence Intervention and study procedures were presented, and feedback was elicited regarding their relevance. We asked about general reaction to game content (including the title and all screens), and we looked for deeper or more complex emerging themes to guide game and procedure development. For example, if certain game actions were more appealing to participants, then this action style was enhanced or increased. When characters were needed with darker or lighter skin or more or less colorful clothing or gender differentiation, we added these game options. All interviews were audiotaped, and major topics and subtopics from the interviews were coded and reviewed.

Approximately 10 participants were shown the storyboard of the game for approximately 30 minutes; qualitative feedback was elicited, and game development for the iPhone occurred. After the development of the iPhone version of *Viral Combat*, 9 of the 20 participants played the game. These 9 participants were shown each of the game levels on the phone by the interviewer and were then able to play each level on their own. After playing the game, these 9 participants completed qualitative interviews, and written or quantitative feedback was obtained. Quantitative feedback was collected from these participants using versions of the Client Service Questionnaire (CSQ-8) [56] and Session Evaluation Form (SEF) [57]. Both of these instruments were developed to measure client satisfaction and perspectives on intervention aspects. Responses to items on these questionnaires helped determine the initial feasibility and acceptability of the intervention. If the gaming intervention consistently received low CSQ-8 or SEF scores (<24 on the CSQ-8 and <30 on the SEF) it was modified until scoring on these measures improved above stated thresholds. Based on these data, *Viral Combat* was modified by Mission Critical Studios to create a final version of the multilevel gaming intervention for the RCT.

Randomized Controlled Trial

Overview

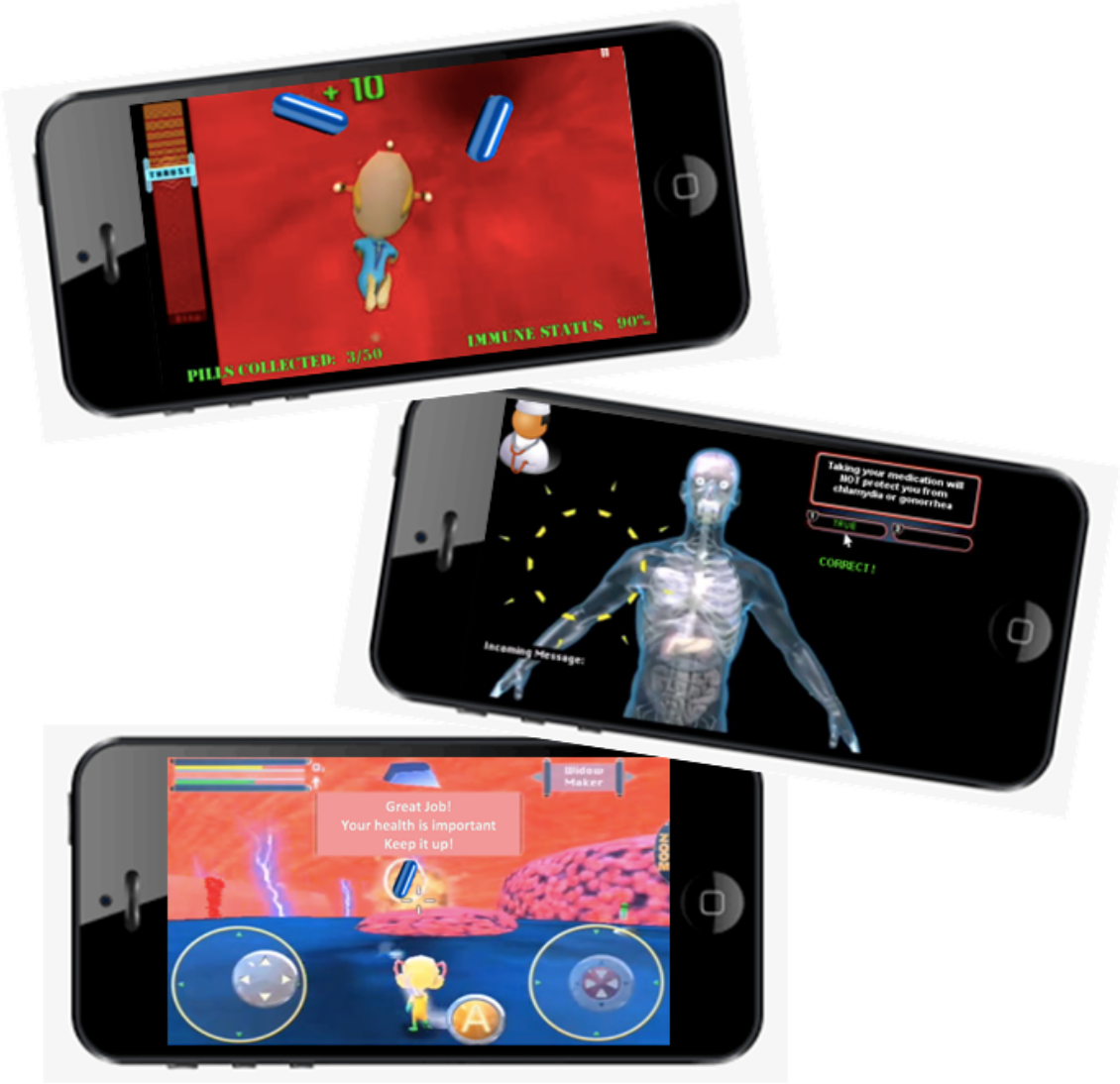
During the RCT phase, we evaluated the preliminary impact of the gaming intervention compared to a comparison group (iPhone with non-PrEP comparison game) using a parallel design with 60 participants on PrEP. Recruitment, enrollment, and implementation of the intervention were conducted in a rolling manner. Randomization (1:1) occurred after enrollment using a computerized, random assignment program. Research staff performed randomization, so the allocation sequence was unknown to the participants and UMMC staff conducting the recruiting. However, the trial was not blinded.

Each participant in the RCT received an iPhone with a paid data service plan for the study duration (iPhone 4S; US $100; US $60/month data package through Lifespan/AT&T). Participants in both arms were given phones because at the time of study commencement, iPhone ownership was not ubiquitous in this clinical population. Participants were able to keep the phone at the end of the study, but the data service plan was not continued. Both the intervention and control games were downloaded at no cost from the App Store onto the iPhones provided to participants at time of enrollment. Participants, therefore, could access the game from any location, at any time. There were no prompts nor reminders sent to participants to play the game. Neither game allowed for communication between participants and study staff. Study staff members were not blinded to condition in the RCT phase of the study. Study staff had limited contact with participants during RCT assessments, as these were done online through REDCap.

Viral Combat Gaming Intervention

The gaming intervention, shown in Figure 2, was designed to improve information, motivation, and skills regarding adherence and HIV preventative behaviors throughout play. All content was chosen for its appropriateness for the target population with refinements made during the developmental phase. With input from the research team and PrEP users, we produced a sensitive, stylistically and theoretically consistent intervention. Each level in *Viral Combat* provides new challenges and unique and colorful environments. Throughout the gaming intervention, subjects continued routine clinical care visits and HIV testing (as recommended by PrEP prescribing guidelines) in the PrEP clinic.

Figure 2. Images from the app/game Viral Combat.



Comparison Condition (Non-IMB iPhone Game)

The comparison condition was matched with the multilevel gaming intervention for appeal, time, and attention. Subjects in the comparison condition received smartphones with the same data service plan as the intervention arm. Smartphones given to participants in the comparison condition had a stylistically similar non-PrEP, non-IMB game designed by the same company, Mission Critical Studios [58]. This was the same game from which *Viral Combat* was adapted. This similarity was important as qualitative assessments did not assess participants' reactions to the control game. The iPhone game in the comparison condition had a look and feel that was very similar to the intervention game but lacked IMB-related, PrEP-related, and HIV prevention–related content in order to control for attention, time, and any influence the receipt of a smartphone or game had on adherence behaviors or the physician-patient relationship. Notably, participants in the comparison condition could hear from those in the IMB intervention about the IMB app/game, but they did not have access to it on their phone. Although it was possible that the participants in the comparison condition could play the game once on an intervention participant's smartphone, it was unlikely to be a frequent occurrence. Nevertheless, we assessed familiarity and usage of the game by self-report at follow-up. In addition, we assessed the occurrence of cross talk between subjects in the two conditions at all follow-ups by asking those in the intervention condition, "Have you spoken to anyone about the game you played in the study (yes or no)?" and for those in the comparison condition, "Have you spoken to anyone about a game related to PrEP (yes or no)?"

Measures and Assessments

All assessments took place in a quiet, private room near or in the PrEP clinic. Assessments occurred at baseline, 12 weeks post-enrollment, and 24 weeks post-enrollment and took 45 minutes to complete.

An audio-assisted computer self-interview using REDCap was used to assess behavior since it was confidential, allowed for complex branching and skip patterns, and detected greater rates of risk behavior [59]. Standard instruments were administered to gather demographic data (including age, level of education, sexual orientation, socioeconomic status, race, ethnicity and stability of housing). The measures listed in Table 1 were used to evaluate HIV-related and STI-related knowledge, attitudes, and risk behaviors.

Table 1. Linkage between constructs, intervention foci, and assessment instruments.

IMB[a] constructs	Intervention foci	Assessment instruments
Information: HIV and STI[b] sexual risk knowledge	HIV knowledge, perceived vulnerability to HIV/STIs	HIV/STI knowledge scales
Motivation: adherence and risk attitudes, intentions, and self-efficacy	Motivation for adherence, motivation for safer sex	Self-efficacy for adherence and sexual safety, adherence and risk attitudes
Behavior: medical adherence, sexual risk, and substance use	Decrease in perceived barriers, increased medication and visit adherence, safer sex skills	Adherence and sexual risk self-report, ARV[c] levels

[a]IMB: Information-Motivation-Behavioral Skills.

[b]STI: sexually transmitted infection.

[c]ARV: antiretroviral.

Primary Outcomes

The primary outcomes included intracellular levels of TFV-DP and emtricitabine (FTC-TP) in red blood cells, as measured using dried blood spots. TFV-DP levels provided a measure of long-term adherence over the preceding month (like hemoglobin A1C), and a detectable FTC-TP level provided information about recent dosing (ie, if FTC-TP was detectable, a recent dose was ingested). The level of intracellular TFV-DP was used to estimate how many doses per week the participant took on average (eg, 7 doses per week, 4-7 doses per week, 2-4 doses per week, <2 doses per week). To collect TFV-DP and FTC-TP levels, 25 µL of blood was drawn from a finger prick.

Secondary Outcomes

The secondary outcomes described in this section were collected from self-report using online questionnaires or from abstraction from medical records. Changes in self-reported measures were evaluated at 12 weeks and 24 weeks.

Self-report of PrEP adherence consisted of the following 3 items developed by Wilson et al [60] that ask about adherence in the past month: (1) “On average, how would you rate your ability to take PrEP as your doctor prescribed?” (2) “How often did you take PrEP as your doctor prescribed?” and (3) “What percent of the time were you able to take PrEP as your doctor prescribed?”

To collect medical history at both follow-up assessments, research staff at the STI/HIV testing clinic abstracted from the electronic medical records, with participant consent, the number of PrEP-related medical visits kept and missed in the past 12 weeks.

The Risk Behavior Assessment is a reliable and valid computer-assisted structured interview used to assess self-reported sexual behaviors. It assesses types of sexual behavior (ie, anal, oral, vaginal) in the past 12 weeks, frequency of sex, and number and gender of partners. Additional questions cover condom use, sex with high-risk partners, frequency and quantity of substance use, and having sex while using alcohol and drugs [61].

To assess HIV knowledge, we used the HIV Knowledge Scale, which assesses knowledge about issues such as risks for HIV using 18 items with “true,” “false,” or “do not know” as response options. Test-retest reliability (r=0.73) and internal consistency (reliability coefficient=0.90) were satisfactory in studies with at-risk young adults [62]. To assess STI knowledge, we used the STI Knowledge Questionnaire, which uses similar response options for 10 items that assess risk for and treatment of STIs. Test-retest reliability (r=0.88) and internal consistency (reliability coefficient=0.86) were both satisfactory in studies with at-risk young adults [63].

The Attitudes towards PrEP Adherence checklist originated from attitude items used in several AIDS clinical trials groups and was modified to reflect adherence to PrEP. The checklist assessed 16 common barriers and 10 facilitators to taking ARV as prescribed.

Motivational readiness for adherence to PrEP and PrEP-related medical visits was assessed using Rollnick’s Readiness Ruler [64]. Respondents rated how ready they were to take PrEP as prescribed and to go to PrEP-related medical appointments on a scale of 1 (not ready) to 10 (ready to be consistent or already consistent). Subjects also completed the 10-item Likert-style IMB PrEP Motivation Scale from the LifeWindows Project Team. It was modified to assess personal and social motivations for PrEP, rather than ART [65].

The PrEP and appointment self-efficacy measure was developed based on Bandura’s theory of self-efficacy [51] and was shown to have strong reliability (reliability coefficient >0.8) in a study of HIV medication adherence [66]. The instrument consists of Likert-style items (with 5 response options): 3 items assessed self-efficacy for taking PrEP as prescribed, and 3 items assessed self-efficacy for attending PrEP-related medical appointments. The IMB PrEP Behavioral Skills Scale has 14 Likert style items and was modified to assess perception of the ability to perform necessary PrEP skills rather than ART skills. It has an internal consistency of 0.9 when use with infected adults [65].

Moderators

In addition to demographic factors, several psychosocial factors may influence adherence, so the project assessed these factors for exploratory analyses to further characterize the sample. Some factors, such as the quality of the relationship with health care providers could function as a moderator or could be influenced by the intervention.

The 5-item relationship with providers measure assessed the perceived relationship with health care providers using

Likert-type items suggested by an ART adherence intervention with adults (Project HEART) [67].

The 6-item social support for medication adherence measure assessed social support for taking medications, going to medical appointments, and other tasks related to adherence using Likert-style items with a 4-point scale. It is being used in AIDS clinical trials. A single score for social support can be generated from these items, or single items can be analyzed, such as support for medical appointments [68].

Mental health issues were assessed using the Brief Symptom Inventory, which requires only 8-10 minutes to complete. It yields 9 primary symptom scales and global indices and has norms for adolescents and adults. The reliability, validity, and utility of the Brief Symptom Inventory instrument have been tested in more than 400 research studies. Internal consistency for the subscales (dimensions) ranges from 0.71 to 0.85 [69].

The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST V2.0) is an 8-item questionnaire that screens for all levels of problem substance use. The instrument covers tobacco, alcohol, cannabis, cocaine, amphetamine-type stimulants (including ecstasy), inhalants, sedatives, hallucinogens, opioids, and "other drugs." The ASSIST V2.0 demonstrates significant concurrent, construct, predictive, and discriminative validity. The ASSIST scores are comparable with other measures of substance use and are able to discriminate between low-risk, moderate-risk, and high-risk use [70].

Statistical Analysis

Hypothesis One

The multilevel gaming intervention was judged by participants to be feasible, appealing, relevant, and useful. A total of 20 qualitative interviews during the developmental phase assessed acceptability and appeal of the intervention. We reviewed the interviews for any game material that was unfavorable to participants and made revisions. Any game modules that received a mean score <20 points on the SEF (smaller scores indicate less satisfaction) were reviewed to determine what content should be revised, changed, or discarded.

Hypothesis Two

Compared to subjects in the control group, participants in the multilevel gaming intervention are anticipated to show improved adherence, improvements in biological measures (higher blood levels of TFV-DP and FTC-TP), decreased HIV risk behaviors, greater increases in HIV knowledge, and improved self-efficacy and attitudes for treatment adherence compared to those in the comparison condition. Generalized estimation equations with a Poisson distribution and log link function will be used to model outcomes with a count distribution (self-report of adherence, unprotected sex, medical appointments). The generalized estimation equation analysis will account for nesting of assessments within participants and allows for data that follow nonnormal distributions. The IMB constructs and levels of TFV-DP are continuous variables and will be evaluated using repeated measures analysis of variance. FTC-TP levels reveal a recent ingestion (yes/no) and will be analyzed by tests of proportional difference. In all analyses, we will test for differences in linear change over time between intervention and control groups on each outcome variable. We will examine baseline differences across all outcome measures to assure that randomization was successful and that groups were equivalent at baseline. We will control for demographic variables that show pretest differences. Hierarchical linear modeling analyses are robust in cases of few missing data. However, if there is a large amount of missing data, last observation carried forward techniques will be employed to deal with attrition and missing values. Outcomes like attendance at a PrEP services appointment can be extracted from medical records, regardless of subject attrition.

Power

As this is an intervention development study and the impact of the experimental intervention is not known, there may not be adequate power to determine the efficacy of the multilevel gaming intervention. Pilot studies are not designed to provide accurate estimates of effect sizes upon which to base large trials [71]. Nevertheless, the pilot RCT may provide a "signal" of impact on outcomes and IMB constructs. Power was estimated using Monte Carlo simulation in Mplus 7.11. We assume 85% retention over the trial period. For the primary outcome, assuming an initial rate of 16 doses per month, this study will have a power of 0.80 to detect a rate ratio of 1.28. In other words, this study will be able to detect an increase from 16 to 20 doses per month (one additional dose each week), assuming the control group maintains 16 doses per month. For the repeated measures analyses of variance, this study will have power to detect a large effect size (Cohen d=0.80).

Incentives

Subjects were reimbursed US $50 for participating in a qualitative interview during the developmental phase. During the qualitative interview phase, participants were also reimbursed US $5 for every level of the game they completed, up to US $30. During the RCT phase, subjects were reimbursed US $50 for baseline, 12-week, and 24-week assessments. Each participant in the RCT received an iPhone with a paid data service plan for the study duration (iPhone 4S; US $100; US $60/month data package through Lifespan/AT&T). Participants in both arms were given phones, because at the time of study commencement, iPhone ownership was not ubiquitous in this clinical population.

Ethical Considerations

To protect participants' confidentiality, the following measures were taken. Participants' research data were identified using a numeric ID only. Any records containing potentially identifying information were kept secure and separate from other research data. All physical records were kept in a locked file, and electronic data were password-protected. Study materials were only accessible to research staff. Data collection took place in a secure and supervised clinical setting or with Health Insurance Portability and Accountability Act-compliant software (REDCap). All study personnel completed training in Human Subjects Research Protection and Health Insurance Portability and Accountability Act regulations (Collaborative Institutional

Training Initiative Program) and received certification. These certifications were kept current in compliance with hospital policies.

Engagement in game analyses, provided by Mission Critical Studios, was participant nonspecific and generalized. For example, Mission Critical Studios collected data on game usage like any other app or website owner that shows percentage of times players of the game complete levels (eg, 50% of players completed level 5). These data were not linked to a particular participant or phone in use. The phone was designated as owned by Lifespan (the organization affiliated with the study) as opposed to the study participant. The gaming data were not connected nor linked to any participant's name, demographic information, or health status.

To further protect the privacy of the study participants, we obtained a Certificate of Confidentiality from the US Department of Health and Human Services. With this certificate in place, the researchers cannot be forced to turn over identifying information about a study participant in any federal, state, or local criminal, administrative, legislative, or other proceedings. This certificate does not prevent a study participant from volunteering to turn over their research information nor does it prevent researchers from providing research-related information to others when requested by the study participant.

Results

This is an ongoing study. Approval was obtained from the affiliated institutional review board in February 2015. Research activities began in June 2015 and are still ongoing. Therefore, we cannot yet report on the effect of the intervention on the desired outcomes. Results will be available at a later date.

Discussion

Review

The use of ARV medications, such as PrEP, to reduce the risk of acquiring HIV infection is a promising prevention strategy. Optimal PrEP treatment requires simultaneous medical care and behavioral interventions to promote adherence and safer sexual behaviors. For interventions to be successful, they must be targeted to populations most at risk, as well as engaging and theory-driven. If *Viral Combat* proves to be effective in future trials, the intervention would be easy to scale up to larger clinical settings.

Limitations

This study had limitations. The trial was unblinded; participants were aware of their study arm assignment, which could influence how they reported on outcomes of interest. Time spent gaming was collected by self-report, and individualized paradata were not collected. Therefore, individual participant's playing time and engagement with the game were not verified. Also, the sample size was small and recruited from the same urban area of the South; therefore, findings may not be generalizable to MSM in other locations.

Conclusion

There are many advantages to using newer interactive technology, such as mobile gaming and text messages, rather than traditional face-to-face counseling, including scalability, efficiency, cost-effectiveness, and appeal. Given the significant health sequelae associated with HIV infections and the paucity of data on PrEP-related adherence and behavioral intervention programs, the knowledge to be gained from this research is significant.

Acknowledgments

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Conflicts of Interest

LM has received honoraria for advisory boards and speaker bureau participation from Gilead Sciences, ViiV Healthcare, and Merck, and his institution has received grants from these companies. Team members were involved in the development of the mobile game for the intervention.

Multimedia Appendix 1
NIH Peer review summary statement.
[PDF File (Adobe PDF File), 155 KB - resprot_v9i9e18640_app1.pdf]

Multimedia Appendix 2
CONSORT EHEALTH checklist (v 1.6.1).
[PDF File (Adobe PDF File), 567 KB - resprot_v9i9e18640_app2.pdf]

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Abbreviations

ART: antiretroviral treatment
ARV: antiretroviral
CSQ-8: Client Satisfaction Questionnaire
FTC-TP: emtricitabine
IMB: Information-Motivation-Behavioral Skills
MSM: men who have sex with men
PrEP: pre-exposure prophylaxis
RCT: randomized controlled trial
SEF: Session Evaluation Form
STI: sexually transmitted infection
TFV-DP: tenofovir diphosphate
UMMC: University of Mississippi Medical Center

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Protocol

Promoting Health and Well-Being Through Mobile Health Technology (Roadmap 2.0) in Family Caregivers and Patients Undergoing Hematopoietic Stem Cell Transplantation: Protocol for the Development of a Mobile Randomized Controlled Trial

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Abstract

Background: Cancer patients who undergo allogeneic hematopoietic stem cell transplantation are among the most medically fragile patient populations with extreme demands for caregivers. Indeed, with earlier hospital discharges, the demands placed on caregivers continue to intensify. Moreover, an increased number of allogeneic hematopoietic stem cell transplantations are being performed worldwide, and this expensive procedure has significant economic consequences. Thus, the health and well-being of family caregivers have attracted widespread attention. Mobile health technology has been shown to deliver flexible, and time- and cost-sparing interventions to support family caregivers across the care trajectory.

Objective: This protocol aims to leverage technology to deliver a novel caregiver-facing mobile health intervention named Roadmap 2.0. We will evaluate the effectiveness of Roadmap 2.0 in family caregivers of patients undergoing hematopoietic stem cell transplantation.

Methods: The Roadmap 2.0 intervention will consist of a mobile randomized trial comparing a positive psychology intervention arm with a control arm in family caregiver-patient dyads. The primary outcome will be caregiver health-related quality of life, as assessed by the PROMIS Global Health scale at day 120 post-transplant. Secondary outcomes will include other PROMIS caregiver- and patient-reported outcomes, including companionship, self-efficacy for managing symptoms, self-efficacy for managing daily activities, positive affect and well-being, sleep disturbance, depression, and anxiety. Semistructured qualitative interviews will be conducted among participants at the completion of the study. We will also measure objective physiological markers (eg, sleep, activity, heart rate) through wearable wrist sensors and health care utilization data through electronic health records.

Results: We plan to enroll 166 family caregiver-patient dyads for the full data analysis. The study has received Institutional Review Board approval as well as Code Review and Information Assurance approval from our health information technology

services. Owing to the COVID-19 pandemic, the study has been briefly put on hold. However, recruitment began in August 2020. We have converted all recruitment, enrollment, and onboarding processes to be conducted remotely through video telehealth. Consent will be obtained electronically through the Roadmap 2.0 app.

Conclusions: This mobile randomized trial will determine if positive psychology-based activities delivered through mobile health technology can improve caregiver health-related quality of life over a 16-week study period. This study will provide additional data on the effects of wearable wrist sensors on caregiver and patient self-report outcomes.

Trial Registration: ClinicalTrials.gov NCT04094844; https://www.clinicaltrials.gov/ct2/show/NCT04094844

International Registered Report Identifier (IRRID): PRR1-10.2196/19288

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KEYWORDS

family caregivers; mobile health app; mHealth; randomized controlled trial; wearable wrist sensor; hematopoietic stem cell transplantation; HSCT

Introduction

Approximately 2.8 million people in the United States are currently providing unpaid, informal care to an adult with cancer [1,2]. With the growing number of cancer survivors, family caregivers represent a critical extension of the national health care system [3]. Caregiving tasks are time- and labor-intensive, and include multifaceted activities [4]. Unfortunately, these experiences may lead to significant physical, psychological, emotional, social, and financial burdens, along with deleterious health effects [5-7]. There is broad agreement that caregiving is challenging and stressful. This is perhaps most pronounced in caregivers of patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT), also commonly known as blood and marrow transplantation, who must address the intense and persistent caregiving needs of some of the most critically ill cancer patients, which continue throughout a prolonged hospital stay, followed by close outpatient follow up over many months [8,9].

Given the high risks associated with HSCT, a dedicated caregiver is necessary and expected for at least the first 100 days post-transplant [10]. However, HSCT caregivers are often unprepared for this role; thus, it is not surprising that HSCT caregivers experience significant levels of anxiety and distress, especially during the peritransplant period [8,9]. Psychoeducation, skills training, and therapeutic counseling interventions have been shown to benefit caregiver health and well-being [11]. However, there remain major barriers in translating successful interventions to clinical practice, including limited understanding of the mechanism of action of an intervention, and need for expert trainers, intensive training, and monitoring [12]. Thus, interventions that are mechanism-focused, low-cost, and sustainable are needed [13].

The ability to capture the hazards of caregiving (ie, adverse physical and mental health consequences) [14] accurately and in real time has been limited by assessments that have traditionally relied on long-term recall and self-report of symptoms. Mobile health (mHealth) technology remains relatively new in the clinical research area, but is spreading quickly and its costs are declining [15], which may facilitate stronger partnerships between patients, family caregivers, and health care providers [16]. In particular, mHealth technology can serve as a platform for the delivery of multicomponent health interventions while capturing continuous, real-time measures via wearable sensors (eg, sleep, physical activity). The extreme HSCT setting [17] provides an ideal “model” to rigorously test an mHealth intervention owing to (1) the high level of engagement by HSCT caregivers; (2) intense and rapidly evolving caregiving needs of medically fragile patients; and (3) long hospital course followed by frequent outpatient follow up that allow for high-resolution data collection with minimal additional burden [18].

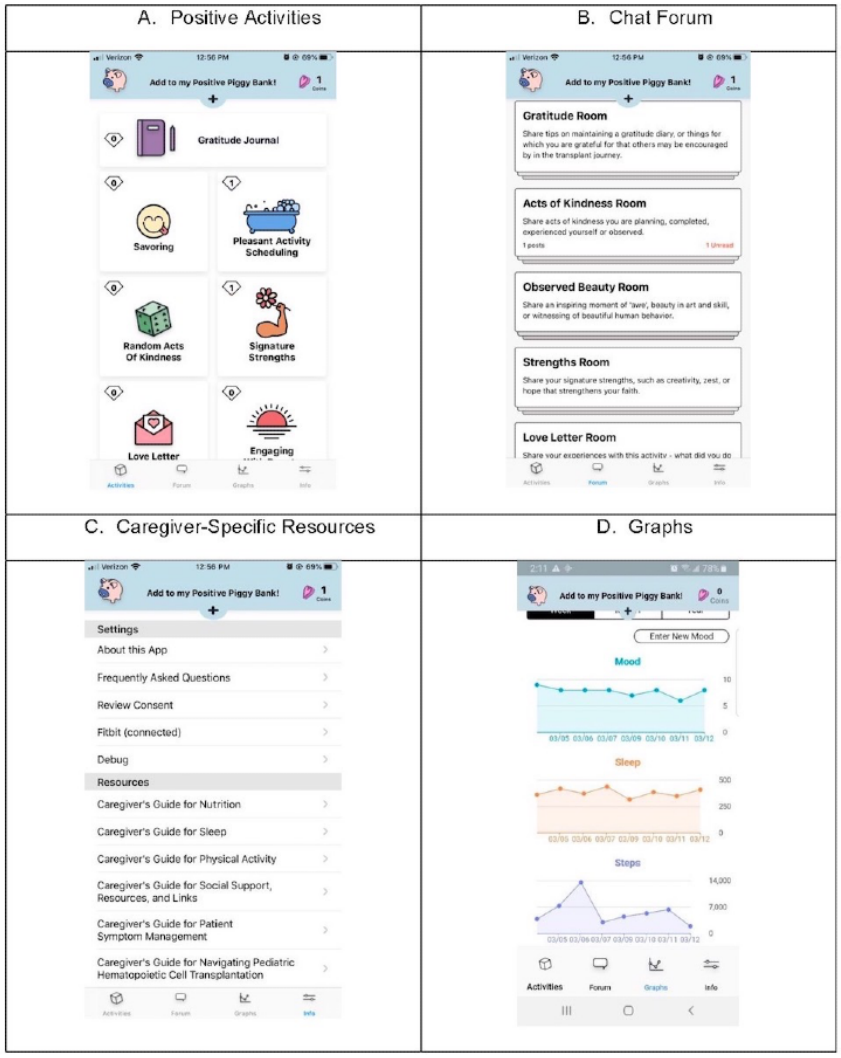
In HSCT, malignant cells are first destroyed by chemotherapy and/or radiation therapy, followed by infusion of compatible donor cells to alleviate profound hematologic toxicities (eg, neutropenia, anemia, and thrombocytopenia) [19]. The main complications, some of which are life-threatening, include mucositis, nausea, vomiting, diarrhea, infections, and bleeding. Therefore, a dedicated 24/7 caregiver is necessary and expected. Frequently, a caregiver is tasked with monitoring treatment side effects, managing the symptom burden, making treatment decisions, administering medications, and performing medical tasks (eg, central line care and dressing changes). After engraftment of donor cells, graft-versus-host disease may ensue, which may further result in prolonged immunosuppression, morbidity, and mortality [20-22]. As such, the HSCT trajectory may be long and unpredictable [23], which creates a complex and multifaceted caregiving process. Caregivers can easily become overwhelmed and must juggle multiple roles: (i) “interpreter” of medical information; (ii) “organizer” of medical appointments and juggling the needs of other family members; and (iii) “clinician” to assess and identify health changes in the patient [23].

Our research team previously developed Roadmap 1.0 (formerly referred to as BMT Roadmap) as a caregiver-facing mHealth app. Details of the app with descriptions of each of the components have been published previously [24-26]. We iteratively designed and developed the Roadmap 2.0 mHealth app following the following 7 research phases: (1) Roadmap 1.0 prototype [27,28]; (2) design groups to evaluate the Roadmap 1.0 prototype [29]; (3) pilot study of Roadmap 1.0 [30-32]; (4) extensive literature review [33,34]; (5) design and development of Roadmap 2.0 in the outpatient setting [25]; (6) design and development of Roadmap 2.0 in the participant home

setting [24]; and (7) deployment of a National Caregiver Health survey [25]. Figure 1 shows screenshots of key app features, and Multimedia Appendix 1 provides a detailed definition of the multicomponent features of the Roadmap 2.0 app.

Our preliminary data showed that family caregivers were interested in and willing to engage in positive psychology interventions to reduce stress and improve their health-related quality of life [18,19]. Herein, we provide a detailed description of the design for a mobile randomized controlled trial to test this investigator-initiated, multicomponent Roadmap 2.0 app comparing a positive psychology-based intervention arm with a control arm in HSCT family caregiver-patient dyads (the Roadmap 2.0 trial). We postulated that simple and intentional pleasant activities that could be developed into routine practices, such as expressing gratitude or scheduling activities that promote positive thoughts, emotions, or behaviors [35-37], may be effective and scalable in the HSCT caregiver population.

Figure 1. Screenshots of the Roadmap 2.0 app.



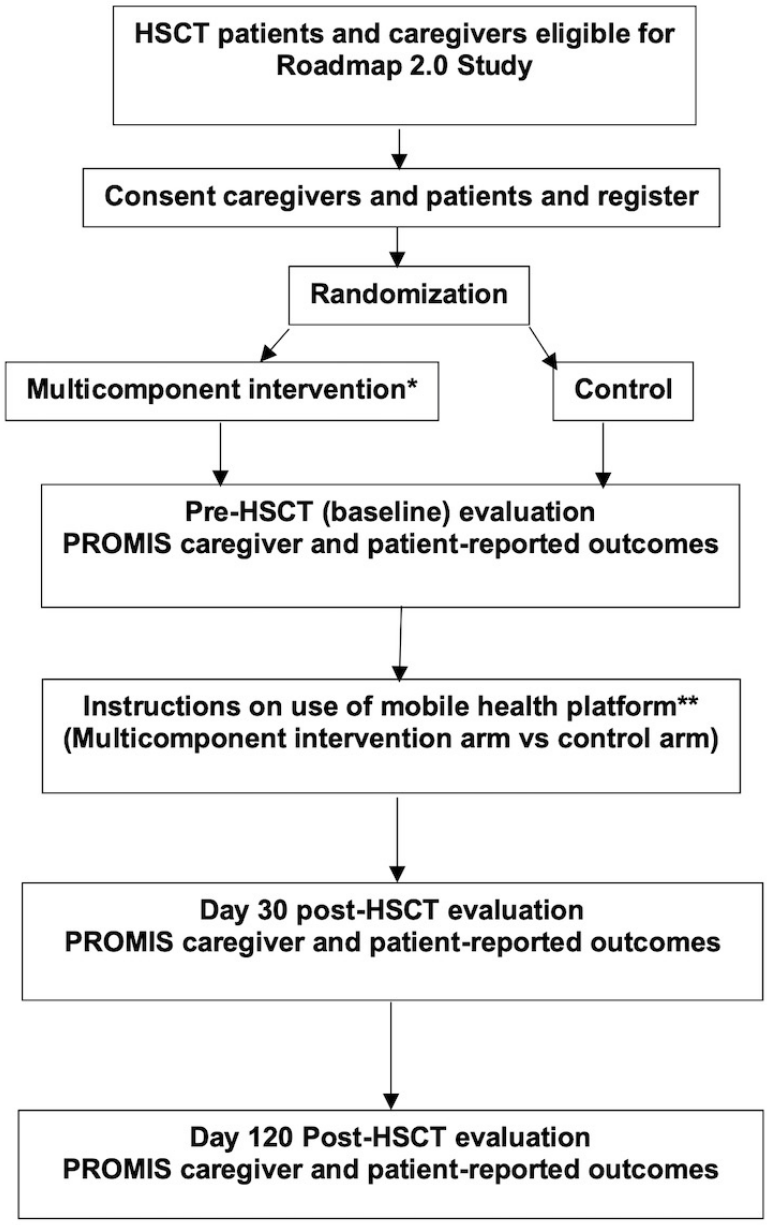
Methods

Study Design

Overview

This study will test the effectiveness of a positive psychology intervention delivered via an mHealth technology platform (see Figure 2 for a schema of the study design). The trial is planned according to a two-arm randomized controlled design. Each of the caregiver-patient participants will be randomized to an active treatment arm (Roadmap 2.0 app + multicomponent features + Fitbit Charge 3) or to a control arm (Roadmap 2.0 app + Fitbit Charge 3; that is, the app displays physiological data only without any multicomponent features). The random allocation of participants to the treatment arm or control arm establishes the basis for testing the statistical significance or difference between the groups in the primary measured outcome (caregiver health-related quality of life, assessed by the Patient-Reported Outcomes Measurement Information System [PROMIS] Global Health scale [38]). Caregiver-patient age, gender, and other prognostic baseline characteristics that could potentially confound an observed association, including those that are unknown or unmeasured, will be distributed equally, except through chance alone, through random assignment. Thus, this design is well-suited to our goal of assessing the effectiveness of an mHealth intervention, Roadmap 2.0, on caregivers (Figure 2).

Figure 2. Study schema. HSCT: hematopoietic stem cell transplantation.



Primary Objective

The primary objective of this proposal is to test Roadmap 2.0 + multicomponent features in caregivers of patients undergoing HSCT. One half of the caregivers will be randomly assigned to the treatment arm and the other half will be assigned to the control arm.

Primary Endpoint

A single primary endpoint of caregiver health-related quality of life (as assessed by the PROMIS Global Health-10 scale [38]) at day 120 post-transplant is designated for the purpose of planning the sample size (see below) and duration of the study, and to avoid problems of interpreting tests of multiple hypotheses (for caregivers and patients).

Secondary Endpoints

Constructs of both caregiver and patient health-related quality of life include (1) positive aspects of caregiving, assessed by the PROMIS Companionship [39], PROMIS Self-Efficacy for Managing Symptoms [40], PROMIS Self-Efficacy for Managing Daily Activities [41], and Neuro-QoL Positive Affect and Well-Being scales [42]; (2) negative aspects of caregiving, assessed by the PROMIS Sleep Disturbance [43], PROMIS Depression [44], and PROMIS Anxiety scales [39]; and (3) other caregiver-specific well-being or health-related quality of life measures assessed by the TBI-CareQoL Caregiver Anxiety [45,46] and TBI-CareQol Caregiver Strain [45,47] scales (see Multimedia Appendix 2). Additional secondary endpoints will include both caregiver and patient health care utilization (eg, total count of hospital days, readmissions, and ambulatory care clinic visits within the first 120 days post-transplant) and patient infections, graft-versus-host disease, relapse, and survival.

Blinding

Study arm assignments cannot be blinded to the investigators because it will be known whether participants have Roadmap 2.0 on their mobile device or not (for technical purposes).

Intervention Period

The intervention will be delivered from the time of admission for the patient's HSCT through day 120 post-transplant. Data will be collected preintervention (baseline), during the intervention (day 30 post-transplant), and at the end of the intervention (day 120 post-transplant). The length of the intervention is therefore approximately 16 weeks.

Participant Enrollment and Evaluation

Participants (caregiver-patient dyads) will be approached for inclusion in the study after the decision to proceed with transplantation is made by the patient. Caregivers will be identified by the patient as their primary caregiver who will be providing at least 50% of the caregiving needs. Multiple caregivers are not allowed according to the study design. Participants willing to participate in this trial will sign an Institutional Review Board (IRB)-approved consent form. Transplant physicians will evaluate the patient eligibility to undergo HSCT as well as eligibility for randomization in this study. Eligibility criteria will be verified by the study team and the clinical trials support office. Ineligible participants will proceed off study and no further follow up will be obtained. The study team personnel (eg, research coordinator) will record the documentation of subject consent in the OnCore Clinical Trials Management System (a web-based system that supports all aspects of clinical research, including protocol management, patient registry, biospecimen repository, and budget tracking) and will be registered through the clinical trials support office.

The inclusion criteria for the caregiver are that they must have an eligible patient (see definition below) for whom they provide at least 50% of care needs, be at least 18 years old, able to read and speak English, and capable of signing an informed consent form. An eligible patient is one who: identifies the eligible caregiver as their primary caregiver (ie, provides at least 50% of their care needs), aged ≥18 years, scheduled to undergo HSCT, and able to read and speak English and to sign informed consent forms.

Patients and caregivers will agree to provide regulatory compliance and IRB-approved informed consent, in accordance with the Clinical Practice Guidelines of the University of Michigan Transplant Program. A patient is considered to be able to undergo HSCT at the University of Michigan only if a designated family caregiver (eg, parent, adult children, spouse, family member, neighbor, friend) accepts the roles outlined in the University of Michigan Caregiver Responsibility Contract, and both the caregiver and patient sign the contract. The exclusion criterion is therefore a patient who does not meet these eligibility criteria to undergo HSCT at the University of Michigan Transplant Program.

Transplant Protocol Registration

Before randomization, the research coordinator must state the baseline caregiver biological characteristics (eg, age, gender, race/ethnicity) through the OnCore Clinical Trials Management System. This will avoid potential biases such as preferential use of gender in one arm of the study. At this stage, the research coordinator will also verify that the patient is still a candidate for transplantation, and that both the caregiver and patient are eligible for the trial.

Randomization

Blocked randomization will be used to limit bias and achieve an equal distribution of participants to the control and treatment arms. Randomization will be overseen by the study statistician (TB).

Once the caregiver is deemed eligible and has provided written informed consent, the research coordinator will confirm their eligibility. The study statistician (TB) will create a randomization list before enrollment using the R statistical software package. The statistician will then forward the list to the clinical trials support office, who will be responsible for enrolling patients and assigning them to the correct study arm. Caregivers will not be randomized more than 21 days from the planned initiation of conditioning. All patient treatments related to the transplant will be scheduled *prior* to randomization. This includes planning an admission date and ensuring that donors can be used in a coordinated fashion with the planned transplant.

Participants (caregiver-patient dyad) randomized to the treatment arm (Roadmap 2.0 app + multicomponents features + Fitbit Charge 3) will be instructed on how to operate the Roadmap 2.0 app on their own mobile device and to create a password, and to use it freely throughout the intervention period. The caregiver and patient will receive their own respective passwords. Timestamps will be recorded of each participant's use of Roadmap 2.0 (ie, number of logins and pages viewed, when and how long and in what order). Caregivers and patients will both be provided with Fitbit Charge 3 wearable wrist sensors.

Participants randomized to the control arm (Roadmap 2.0 app without any multicomponent features + Fitbit Charge 3) will be advised to use their own mobile device freely throughout the intervention period. Participants will receive usual care, defined as standard-of-care information provided according to the Clinical Practice Guidelines of the University of Michigan Transplant Program. This version of Roadmap 2.0 has no positive psychology-based activities, but caregivers and patients will both be provided with Fitbit Charge 3 wearable wrist sensors. Their view of the app will only include the "Settings" section but not the "Resources" section (Figure 1).

Confidentiality

Confidentiality will be maintained by individual names being masked and each participant being assigned a patient identifier code. The code relaying the participant's identity with the ID code will be kept separately at the Clinical Trials Support Office. The outcome measures will be deidentified and masked to the biostatistician/data scientist performing the analyses.

Pretransplant Evaluations

Based on prior work, our study team has experience in obtaining caregiver demographics. The following data will be collected

(ie, caregiver self-report) via the Roadmap 2.0 app within 30 days of randomization: demographic, caregiving, and personal health variables such as marital status, alcohol/tobacco use, education, employment, annual household income, use of technology, type of relationship to the patient, number of household members, health insurance status, number of years and number of hours per week (of caregiving), health comorbidities, medications, and caffeine intake.

The following data will be collected within 30 days of randomization, according to the Transplant Program Clinical Practice Guidelines in patients undergoing transplant: history, physical examination, height, weight, Karnofsky performance status [48], HSCT-specific Comorbidity Index Score [49], routine laboratory parameters (eg, complete blood count with differential and platelet count, serum creatinine bilirubin, alkaline phosphatase, aspartate transaminase, and alanine aminotransferase), infectious disease titers, electrocardiogram and left ventricle ejection fraction, pulmonary function tests, disease evaluation of underlying blood disease, chest X-ray or chest computed tomography, pregnancy test, pretransplant donor and recipient samples for post-transplant chimerism evaluation, and pretransplant blood samples for future research.

PROMIS caregiver and patient health-related quality of life assessments will be obtained at baseline, preintervention (Multimedia Appendix 2).

Intervention

Overall Design

Participants (caregiver-patient dyad) who are consented, enrolled, and randomized in the study will be scheduled for a 1-hour virtual video training session with the research coordinator prior to admission to undergo the transplant. Based on our experience, these training sessions will be coordinated with other clinic appointments at the hospital in efforts to minimize the burden on the caregiver and patient. Once the intervention has begun, the research coordinator will meet with the participants (caregiver-patient dyad) weekly (virtually) to review any questions or concerns and to ensure adherence to the protocol. HSCT patients are typically inpatients for approximately 4 weeks. During this period, the research coordinator will be available by pager and will schedule weekly visits (virtual or in person if needed) with the participants. Once discharged, HSCT patients return to the clinic on a weekly visit in the ambulatory care setting. The research coordinator will meet with participants during these routine appointments or virtually if possible.

Fidelity

Based on our prior work, it is critical that adherence and fidelity of the protocol are maintained. Thus, our research staff will develop Intervention Fidelity Guidelines (Multimedia Appendix 3) for the study team to follow and monitor participants, which will help to increase confidence that "study outcomes are due to the intervention being investigated and not due to variability in intervention implementation" [50]. Moreover, the Intervention Fidelity Guidelines will assist in future implementation and dissemination efforts. A rigorous Recruitment and Retention Plan has also been developed and will be adhered to according to good clinical practice (Multimedia Appendix 4).

Power Calculation

The power calculation was completed using simulations in the statistical package R. We will enroll 166 caregivers and their care recipients (332 total individuals). Our primary endpoint (ie, caregiver health-related quality of life from the PROMIS Global Health scale) is focused solely on this outcome in caregivers, whereas our secondary endpoints are based on outcomes for both caregivers and patients. Accordingly, we determined the sample size based solely on caregivers. The age- and sex-adjusted norm for the Global Health scale is 50 points, with a standard deviation of 10 points; these statistics have been shown to be generalizable to the HSCT population. With 67 caregivers enrolled in each arm, our study will have power of 0.80, assuming a two-sided type I error rate of 0.05, to detect an effect size of 0.5 between the intervention and control arms. A mean difference of one-half a standard deviation is biologically meaningful and is considered a medium effect size for clinical trials. We will accrue a total of 83 caregivers in each arm to account for dropout, assuming a 5% failure to undergo HSCT, 8% death before day 120, and 10% missing day 120 patient-reported outcomes from participants.

Data Analysis

PROMIS measures are based on the item response theory [51], a family of statistical models that link individual questions to a presumed underlying trait or concept of global health represented by all items in the scale. PROMIS instruments are scored using item-level calibrations. The most accurate way to score a PROMIS instrument is to use the HealthMeasures Scoring Service, which our study team has prior experience with. This method of scoring uses "response pattern scoring," which scores the responses to each item for each participant. Response pattern scoring is especially useful when there are missing data (ie, a respondent skipped an item, or different groups of participants responded to different items).

Visit Schedule (Occurring and Planned Visits)

The study intervention period includes the time of admission to the transplant unit through day 120 post-transplant. The average length of hospitalization is 4 weeks. The research coordinator will meet with study participants once weekly during the inpatient hospitalization period. Following discharge, the research coordinator will continue meeting with study participants during routine, standard-of-care weekly visits through day 120 post-transplant (study endpoint). Baseline, day 30, and day 120 post-transplant survey instruments will be completed by study participants.

Data and Safety Monitoring

This study will be monitored in accordance with the University of Michigan Data and Safety Monitoring Plan for HSCT-specific study protocols. The study team will meet every 6 months or more frequently depending on the activity of the protocol. The discussion will include matters related to the safety of study participants (adverse event and severe adverse event reporting), validity and integrity of the data, enrollment rate relative to expectations, characteristics of participants, retention of

participants, adherence to the protocol (potential or real protocol deviations), and data completeness. At these regular meetings, the protocol-specific Data and Safety Monitoring Report form will be completed and signed by the principal investigator or by one of the coinvestigators. Data and Safety Monitoring Reports will be submitted to the University of Michigan Data and Safety Monitoring Committee and the IRB every 6 months for independent review.

Results

The study protocol complies with the Declaration of Helsinki. This protocol has been approved by the IRB at the University of Michigan and has been registered at ClinicalTrials.gov (NCT04094844).

Due to the current COVID-19 pandemic [52,53], the study has been briefly put on hold. However, recruitment began in August 2020. We have converted all recruitment, enrollment, and onboarding processes to be conducted remotely through video telehealth. Consent will be obtained electronically through the Roadmap 2.0 app.

Discussion

Caregiver burden is defined as a "negative reaction to the impact of providing care on the caregiver's social, occupational, and personal roles" [54]. To date, substantial focus has been placed on the wide range of *negative* implications associated with caregiving [55] (eg, depression, anxiety) [56]. Nevertheless, a majority of caregivers have recognized the benefits of caregiving [57,58]. The imbalance of focusing primarily on negative aspects may limit our ability to develop new assessment and intervention methods [59]. Thus, a "corrective focus" is needed in caregiving research to expand knowledge on the *positive* aspects of caregiving [60,61]. Research on self-management suggests that self-efficacy, a positive aspect, can promote caregiver health, well-being, and positive health behaviors (ie, improved sleep and physical activity) [62,63].

The positive aspects of caregiving, such as self-efficacy and positive attitudes toward the caregiver role, may explain how caregivers can positively engage patients in self-care activities [64]. Caregivers with better self-efficacy and well-being (eg, health-related quality of life) may positively impact patients' health outcomes [65-67]. Simple strategies aimed at enhancing positive thoughts, emotions, and behaviors have been shown to be effective and highly scalable [35-37]. Positive activity interventions such as daily positive reflection, gratitude journals, and conducting acts of kindness have been used in the context of heart disease, cancer, diabetes, and chronic pain [68-73]. Our preliminary data suggest that HSCT caregivers desire these activities to reduce stress and improve well-being.

Caregivers experience significant stress, anxiety, and poor sleep that lead to physiological changes [74]. Indeed, long-term caregiving has been associated with increased physical morbidity [75]. Although caregiver interventions have been shown to reduce emotional distress and increase well-being [76], less is known about the impact of physiological changes on caregiver health and well-being [14]. Previous caregiver assessments have relied on snapshot self-report measures (ie, patient-reported outcomes) [77]. Recent advances in wearable sensors facilitate the noninvasive collection of continuous, real-time measures (eg, sleep, physical activity). These highly time-resolved, objective parameters correlated with subjective patient-reported outcomes may help us to further identify the mechanism of action of an intervention. Further, newer data science techniques may enable data patterns, relationships, and interpretation in ways that were not previously possible [78].

Emerging literature on family caregivers suggests a wide range of health information technology studies that are being conducted [79-82], which have been embraced by both caregivers and patients [16]. We have described the design and research protocol of an mHealth app for HSCT caregivers and patients, which will be tested in a Roadmap 2.0 mobile randomized trial. We outlined the multicomponent features of the mHealth app, study design, inclusion/exclusion criteria, how the intervention will work, recruitment and retention, intervention fidelity guidelines, and data safety monitoring plans. Our multicomponent intervention is innovative, and our mHealth app could have significant impact and wide-ranging clinical applications. Alternatively, even if the primary endpoint of the intervention is not met, we will be able to use the caregiver and patient experiences and secondary outcome findings to create new hypotheses and explore alternative strategies. We are excited about the large multiparameter dataset that will be collected from diverse sources, including caregiver- and patient-reported outcomes, interviews, and physiological markers. Thus, the data streams of Roadmap 2.0 have the potential to provide new understanding about what component of the intervention is driving a desired or undesired outcome. Furthermore, this study has potential to generate new insights into the relationship between caregiver burden, well-being, and health without the dependence on expert trainers, intensive training, or monitoring given its remote features. Ultimately, we anticipate that this study will inform more personalized interventions for caregivers and patients in the future, and address gaps in previous interventions that required face-to-face interactions.

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Authors' Contributions

MR and MD were responsible for writing the original draft, data curation, and visualization; AM and MT reviewed and edited the manuscript; AH, DB, NC, and DH were involved in protocol development, study design, and writing-review/editing; TB contributed to protocol development, study design, and the power calculation; SC is in charge of data curation, investigation, methodology, data analysis, resources, supervision, visualization, and manuscript writing and review.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Definitions of multicomponent features of Roadmap 2.0.
[DOCX File , 122 KB - resprot_v9i9e19288_app1.docx]

Multimedia Appendix 2
Caregiver- and patient-reported outcome measures.
[DOCX File , 821 KB - resprot_v9i9e19288_app2.docx]

Multimedia Appendix 3
Intervention Fidelity Guidelines.
[DOCX File , 423 KB - resprot_v9i9e19288_app3.docx]

Multimedia Appendix 4
Recruitment and Retention Plan.
[DOCX File , 15 KB - resprot_v9i9e19288_app4.docx]

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Abbreviations

HSCT: hematopoietic stem cell transplantation
IRB: institutional review board
mHealth: mobile health
PROMIS: Patient-Reported Outcomes Measurement Information System

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Protocol

Mobile-Enhanced Prevention Support Study for Men Who Have Sex With Men and Transgender Women Leaving Jail: Protocol for a Randomized Controlled Trial

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Abstract

Background: Men who have sex with men (MSM) and transgender women, particularly those who have experienced criminal justice involvement, have particularly high HIV burdens, and a majority of those in jail have substance use disorders (SUDs). MSM and transgender women also experience elevated rates of incarceration. Once community re-entry occurs, individuals are in a critical period for addressing potential risks of HIV and sexually transmitted infection (STI) acquisition and negative sequelae of substance use. Further, the impact experienced by one's social and sexual networks experienced at the time of detention and release have important health implications for MSM and transgender women.

Objective: The purpose of this study is to test a new intervention—Mobile-Enhanced Prevention Support (MEPS)—that involves a GPS-based mobile app called GeoPassport (referred to as GeoPass in practice), incentives, and peer support for promoting HIV prevention, substance use treatment, and use of related services.

Methods: A two-arm, unblinded, randomized controlled trial will seek to enroll 300 HIV-negative MSM and transgender women, aged 18-49 years, with SUDs, who are either in jail or have recently left jail. Participants will be enrolled by study staff and randomized to the MEPS intervention group or usual care group. The intervention group will receive customized wellness goals in addition to GeoPass, cash incentives, and the support of a trained peer mentor for 6 months. Data collection will consist of a baseline survey and three follow-up surveys at 3, 6, and 9 months postenrollment, either in person or by phone or videoconference when necessary. The primary outcomes include establishing a primary care provider; being prescribed and adhering to pre-exposure prophylaxis (PrEP) for HIV; screening for HIV, STIs, and hepatitis C virus; and engagement in recommended treatment for SUDs. Secondary outcomes include obtaining treatment for any identified infections and avoiding recidivism.

Results: Enrollment began in November 2019 and study completion is expected in 2023.

Conclusions: This study will advance our knowledge base on patient navigation and peer mentor interventions. Peer navigation services have been studied for the treatment of HIV, but less often in the context of HIV and STI prevention among sexual and gender minority populations at the time of re-entry into the community from jail. The MEPS study will examine the acceptability and feasibility of combining peer mentor services with a mobile app to facilitate service utilization and participant–peer mentor communication. MEPS will assess patterns of PrEP uptake and utilization in MSM and transgender women leaving jail. The study will provide heretofore unavailable data from persons leaving jail regarding HIV PrEP, STI screening, substance abuse treatment, and service utilization patterns and experiences, including geocoded data for those in the intervention arm.

Trial Registration: ClinicalTrials.gov (NCT04036396); https://www.clinicaltrials.gov/ct2/show/NCT04036396

International Registered Report Identifier (IRRID): PRR1-10.2196/18106

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KEYWORDS

HIV; MSM; transgender women; peer navigation; jail; substance use disorder; eHealth; PrEP; sexually transmitted infections; hepatitis C; mobile phone; smartphone

Introduction

In the United States, men who have sex with men (MSM) and transgender women face myriad and overlapping risks to their health and well-being. MSM and transgender women are disproportionately impacted by HIV, hepatitis C virus (HCV), and other sexually transmitted infections (STIs). In 2017, 70% of the new HIV diagnoses were among gay and bisexual men, and the majority of those individuals were non-White [1]. Transgender individuals face an HIV prevalence of 1.4%, nearly five times higher than that of the general population (0.3%), with the number going up to 19% when focusing on Black transgender women specifically [2]. MSM also face increased incidence of other STIs compared to men and women who have sex with women only [3]. A recent systematic review reported a high prevalence of other STIs among transgender women but noted that most of the studies were focused on sex workers and may not be representative of the larger population of transgender women [4]. MSM and transgender women populations generally are at increased risk of developing substance use disorders (SUDs) [5,6].

Those who have experienced criminal justice involvement have particularly high HIV burdens. MSM HIV prevalence estimates in jail populations are higher than in the general US population; in addition, MSM and transgender women populations experience elevated rates of incarceration [7,8]. Several factors contribute to the increased risk of HIV and incarceration among transgender women, including increased rates of survival sex, sex work, and experience of sexual violence [2]. Furthermore, a majority of people in jail have SUDs [9].

The period that begins following community re-entry from jail, or prison, has been associated with risky sexual and substance-using behaviors and is implicated in elevated rates of mortality in populations of people with criminal justice involvement. Among the starkest examples is a study documenting a nearly 13-fold increase in mortality risk in the first 2 weeks after release from a Washington State prison. Much of this excess mortality was attributable to overdose, with cocaine and opiates being the leading cause [10]. For MSM, recent incarceration may disrupt existing relationships and contribute to sexual concurrency [11]. As such, the re-entry period is critical for addressing potential risks of HIV and STI acquisition as well as negative sequelae of substance use.

Although some demonstration projects have shown positive results in facilitating linkage to HIV care in the community for those leaving prison, there is a dearth of data about jails specifically [12-14]. Few, if any, randomized controlled trials (RCTs) have been published on effective interventions, particularly for substance-using people living with HIV leaving jail, and, by extension, those at risk for HIV, rather than those leaving long-term prison facilities. A recent RCT tested a peer-based intervention for HIV-positive individuals leaving jail that showed efficacy in preventing declines in viral suppression [15].

The provision of peer navigation services, including accompaniment, assistance with development of behavioral and self-care skills, and coaching clients to enhance patient communication with providers, has demonstrated promising results with HIV-positive patients [15-17]. However, we are not aware of any studies that focus on testing peer navigation services in sexual and gender minority populations with criminal justice involvement.

The purpose of this study is to inform an intervention designed to reach a high-risk population at a critical point for increased risk of HIV infection: MSM and transgender women who have SUDs and are leaving, or have recently left, jail. The study will test a new intervention called Mobile-Enhanced Prevention Support (MEPS) that involves a GPS-based mobile app called GeoPassport (referred to as *GeoPass* in practice), incentives, and peer support for promoting the use of HIV prevention and related services; the intervention will be compared to the case management services that these individuals can routinely access following jail release. It is hypothesized that the intervention will increase rates of service utilization; HIV, STI, and HCV screening; and use of pre-exposure prophylaxis (PrEP) for HIV prevention as compared to the standard-of-care case management, referred to below as the control group.

Methods

Study Aims

The study's primary aims are as follows:

1. Measures of PrEP uptake:
   a. Seek care with a primary care provider who can prescribe PrEP,
   b. Obtain screening for PrEP,
   c. Begin PrEP,
   d. Adhere to PrEP, and
   e. Remain on PrEP for at least 3 months.
2. Sufficient preventative screenings:
   a. HIV screening every 3 months,
   b. Bacterial STIs screening every 6 months, and
   c. HCV screening at least once.
3. Enrollment in appropriate SUD treatment:
   a. Received any SUD treatment postrelease,
   b. Attended some SUD treatment services appropriate to their American Society of Addiction Medicine (ASAM) level, and
   c. Met at least 70% of recommended treatment activities and frequencies for ASAM level of care.

The study's secondary aims are as follows:

1. Obtain appropriate follow-up care for those who test positive for HIV, STI, and HCV.
2. Reduce recidivism during the study period.
3. Describe the temporal and geographic distribution of PrEP uptake and supportive social service utilization patterns of a postincarcerated jail population at high risk for HIV.

Study aims are measured at follow-up interviews that take place at 3, 6, and 9 months postenrollment.

Study Population and Recruitment

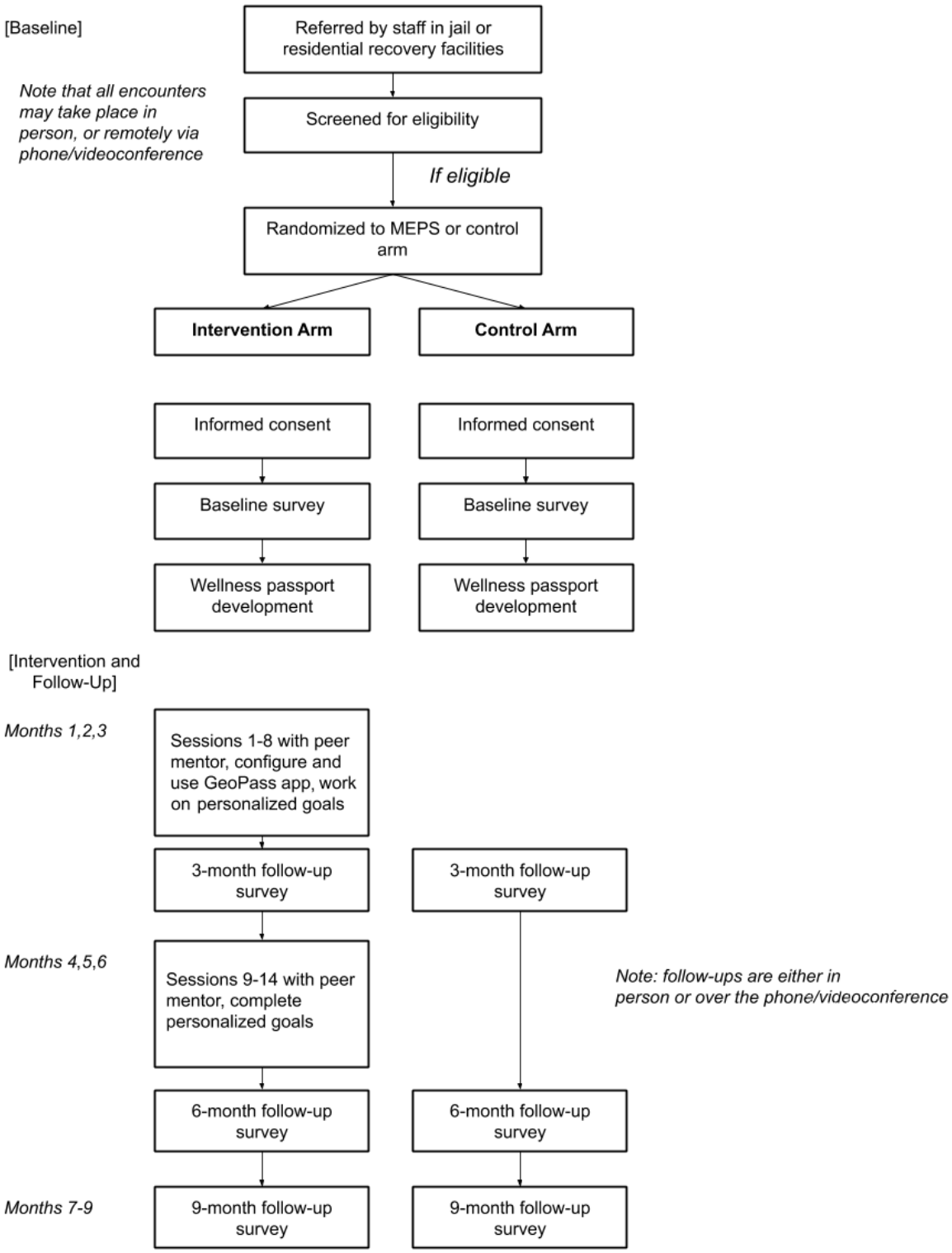
This study will focus on the MSM and transgender women housed in the K6G (Keep Away Designation 6G) unit of the Los Angeles County (LAC) Men's Central Jail and in residential recovery facilities in LAC.

The K6G unit houses individuals who self-identify as gay or bisexual men and transgender women. It is a voluntary unit in which people are housed for their own protection. Initial screening for entry occurs at jail intake. The unit was established based on a documented pattern of abuse of gay- and transgender-identified people by other inmates in the LAC jails. K6G is a protected custody unit, with limited access to other inmates. Individuals must pass additional screening regarding their sexual and/or gender identity to be housed in the unit [18]. The Los Angeles Centers for Alcohol and Drug Abuse (LA CADA) is funded via Medi-Cal (Medicaid in California) to provide SUD treatment services in the K6G unit. They operate the Substance Treatment And Re-entry Transition (START) program (ie, Project START), which was specifically tailored for these populations and includes both in-patient and transitional case management services.

The residential facilities are located throughout the Los Angeles metro area and serve as additional recruitment sites because they provide services to individuals who have recently been incarcerated. The community sites may provide residential treatment, recovery bridge housing, sober living, and/or supportive housing services. A flowchart of the MEPS study can be found in Figure 1.

We will enroll and randomize 300 individuals into the study who are recruited from jail or from residential facilities within 6 months postincarceration. We will conduct a trial comparing a control group (n=150) that is assigned to receive usual care to an intervention group (n=150) that receives GeoPass, incentives, and the support of a trained peer mentor for 6 months. GeoPass will provide participants with tools for tracking goals and progress toward meeting them, assistance in locating services, appointment and medication reminders, opportunities to provide feedback on service providers, and built-in tracking and distribution of rewards (ie, incentives) for service utilization. GeoPass will assist peer mentors in monitoring participants' service utilization. The peer mentors will provide encouragement, role modeling, accompaniment to appointments, and assistance with goal setting, problem solving, and reducing logistical and psychosocial barriers to service engagement. Participants in both groups will be followed to assess whether those offered the MEPS intervention are more likely to utilize specific services.

Figure 1. Mobile-Enhanced Prevention Support (MEPS) study flowchart.



Study Eligibility

Study eligibility inclusion criteria are as follows: (1) housed in K6G unit or incarcerated in the previous 6 months and now residing in a residential facility with services (ie, residential treatment and recovery bridge housing) or supportive housing within 6 months of release, (2) aged 18-49 years, (3) screens positive for SUDs, (4) self-identifies as a man or transgender woman, (5) reports sexual intercourse with a male or a transgender woman in the 6 months prior to jail entry, (6) is likely to remain either in custody if in jail or at a residential recovery facility for at least 4 more days, but if in jail, then less than 3 more months based on scheduled court dates, current sentence, etc, (7) has not received an HIV diagnosis, based on self-report, and (8) plans to reside in LAC for the 12 months following enrollment.

Exclusion criteria are as follows: (1) does not have a smartphone and is not willing to obtain one postrelease, (2) is not able to

speak and understand English, as the intervention is delivered in English, or (3) has insufficient reading skills to operate a mobile app.

For potential participants who do not have a smartphone at the time of enrollment, study staff will work with them to obtain a phone upon enrollment.

Screening, Consent, and Enrollment Procedures

Study staff will communicate with residential facilities to identify potentially eligible participants. Staff at residential facilities, who possess the eligibility criteria, will assist in identifying eligible participants and talking to them about the study, using a brochure produced by the study to help introduce it to potential participants. Facility staff will fill out a referral form that includes a signature from the potential participant indicating their interest in being approached by the study staff. The study staff will arrange to meet the individual. Study staff (ie, a research associate or other member of the team) will meet with potential participants in a classroom area, an office, or another similar, semiprivate or fully private location within the jail or the residential facility. For enrollment by phone or videoconference, the interviewer will screen interested individuals and obtain consent from those who screened as eligible.

For in-person enrollment in jail, each participant will be called in individually and, where required, jail staff or a case manager will escort the participant from their dormitory to this space. Once inside the interview setting, for potential participants in jail, the jail staff will maintain some visual and very limited audio contact. They must maintain some audio contact in case of emergency; however, these personnel will not be able to hear the survey questions or the respondents' answers. Los Angeles County Sheriff's Department (LASD) custody staff will only be told that it is a study to identify the best ways to keep people healthy following release.

The interviewer will introduce themselves and the study using the script in the in-person consent screen. If the individual expresses willingness to learn more after the brief introduction, they will finish the study description and continue with the screening questions. Randomization will coincide with informed consent, with participants learning the results at the same time as the interviewer. We will randomize participants to the two arms at a 1:1 ratio without any other restrictions. The data manager will pregenerate the random allocation sequence using a SAS program (SAS Institute Inc) designed for this purpose. Randomization allocations will be maintained in sequentially numbered, opaque sealed envelopes by the study director and interviewers for distribution as new study participants enroll. Randomization assignments will be opened and given sequentially after confirming eligibility and after consenting participants complete their baseline surveys. For participants recruited remotely, during enrollment, the data manager will send the allocation in an email attachment to be opened by the interviewer.

This double-consent approach has been used to examine the impact of residential substance abuse treatment length on both substance use and HIV risk behaviors [19]. This approach has been selected to minimize dissension and conflict among potential study participants assigned to the study arm that receives incentives and those assigned to the standard-of-care study arm.

After reviewing the consent form for the group to which the study participant was assigned and after providing potential participants with the purpose of the study, the study's goals, potential risks, and safeguards for confidentiality, participants will be given the opportunity to ask questions and have them answered. Moreover, the interviewer will ask the participants questions to confirm their understanding by asking them to explain in their own words what the study entails, along with the study's goals, main procedures, and risks and benefits, using an Evaluation to Sign a Consent Form for Research document produced by Charles R Drew University. Those able to respond satisfactorily will be asked to sign the informed consent form. Others may indicate a lack of interest at any time and return to their dormitories.

A locator form will be used to determine where and how study staff should attempt to reach participants once they leave jail or a residential facility in order to contact them for follow-up surveys and peer mentor meetings. In addition, participants will be encouraged to contact study staff via the study's phone number or email following their release from custody. Release dates of those in jail will be solicited during the interview and tracked on publicly available inmate locator websites to establish target dates for the follow-up interviews, so the study team may reach them for follow-up once they are released from jail. On the locator form, participants will be asked to designate whether or not messages may be left and how they want study team members to refer to the study when leaving messages with their indicated contact information.

Participants will be asked to fill out and sign three release-of-information forms. One form is specific for LA CADA and allows the study team to access START assessments for participants who have gone through Project START. The second form is generic and allows us to contact organizations that the participant identified during the baseline interview. The third form allows future housing facilities to confirm the presence of the participant, should they move there during the study period.

Baseline Assessment

The baseline surveys will be conducted by a trained research associate and may be performed in jail, in a residential facility in the community, or remotely by phone or videoconference as necessary. Participants will complete a 75-minute survey in a classroom, office, or other similar semiprivate or private location. The survey covers the following topics: (1) sociodemographics, (2) criminal justice history and status, (3) HIV and STI knowledge and risk perception, (4) psychosocial factors, such as medical mistrust and social support, (5) substance use, (6) self-efficacy, readiness, and motivation, (7) service utilization and needs, (8) sexual risk behaviors, and (9) health conditions. Most questions are asked during both the baseline and follow-up interviews; others are asked only during the baseline or the follow-up interviews.

In addition, we will collect basic information on participants' current and prior arrests, including reasons for arrest, date of arrest, location of arrest, sentence length, release agency, and disposition codes, as well as some demographic information (ie, age, birth date, and race or ethnicity) from the publicly available LASD inmate locators; we will link this information with the survey data. By matching survey participants with these data, we will augment the surveys with record-based information on participants' criminal justice involvement.

Development of the Wellness Plan

The wellness plan will be based on an auto-generated assessment report from the baseline survey. This report will summarize potential sexual behavior and substance use risk factors; gaps in knowledge regarding HIV and STIs; history of PrEP use; prior testing for HIV, STIs, and HCV; lack of access to primary or mental health care; lack of social support; religious conflict; and unmet needs that the participant experienced prior to incarceration as well as health conditions for which they may need assistance in obtaining care postrelease.

Using the assessment from the baseline survey, the passport developer—either a trained full-time member of the study team or a trained substance abuse counselor from Project START or one of the residential facilities—will work with participants to determine which of the identified concerns they find most problematic and most motivates them to address postdeparture from jail or the residential facility. Goals related to PrEP uptake will vary based on each participant's *stage of change* in this area and may range from accessing PrEP information from preidentified, online sites to reestablishing an existing PrEP prescription upon departure. Activities related to SUDs will depend on the recommended ASAM level of care based on results of assessments for SUDs as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).

The 15-25-minute passport development process will result in a list of at least three specific goals and 8-12 activities that will facilitate reaching those goals, as well as the utilization of at least two of the health services that are part of the study outcomes. The process will also include education to ensure that the participant is aware of the importance of HIV, HCV, and STI testing and treatment; that they are informed about PrEP; and that any reported misconceptions about HIV and STIs that they may have are addressed. The study team will provide participants with a printed copy of each individual's passport, augmented with detailed information on the referral agencies and resources discussed during the passport planning meeting. This passport will also be shared with the case managers of whatever program the participant is receiving residential services from.

The passport development process is rooted in both the transtheoretical model and motivational interviewing. It involves a client-centered approach to identifying participants' needs, priorities, and readiness to change and starting the process of encouraging behavior change. Multimedia Appendix 1 shows a sample of the wellness passport.

Control and Intervention Arms

Control Arm

Participants randomized into the control arm will continue to receive the usual care consistent with the setting they are in (ie, jail, residential treatment, supportive housing, etc). Participants recruited in jail will be enrolled in, or on the waitlist for, the LA CADA Jail Health Services program, called Project START, which is one of only four jail-based SUD treatment programs in LAC and is supervised and funded by the LAC Substance Abuse Prevention and Control Division of the Department of Public Health. Participants enrolled in the community will be housed in residential facilities that provide SUD services or supportive housing.

Mobile-Enhanced Prevention Support Intervention Arm

Overview of Arm

The MEPS intervention is designed to support, motivate, and facilitate engagement in preventive health care activities in the period of community re-entry after departing jail or a residential facility. The intervention involves three components, in addition to the standard of care: support from a selected peer mentor, incentives, and a newly developed mobile app. It is a client-driven approach, in which participants are encouraged to address the priorities and immediate needs that they identify through the app development process, especially social determinants of health that may discourage or undermine preventive health measures. A total of 14 peer mentor meetings are planned, either in person or remotely. Study staff will work with participants and any facilities in which they reside to ensure sufficient internet access to conduct peer sessions remotely, including obtaining a smartphone if needed.

The conceptual model for this peer mentor–led, mobile-enhanced intervention is based on an adaptation of Social Cognitive Theory (SCT) as applied to the ideal continua of care for HIV prevention and substance use. SCT is widely applied in HIV research because it helps explain how people acquire and maintain behavior change [20,21]. SCT underlying the peer mentor intervention holds that factors affecting the prevention continuum include the personal, behavioral, and environmental. Environmental factors include the experience of social support, social stigma, availability of care services, competing basic needs for care, and relationship with providers. The social environment also includes observational learning through peer mentor role models [22]. Personal factors include knowledge about HIV, STI, and HCV prevention as well as treatment for SUDs and the skills to perform and maintain related behaviors [23]. Behavioral factors include self-efficacy, outcome expectations, goal setting, and problem solving. We add the following to the classic SCT variables: barriers to, and facilitators of, HIV, STI, and HCV prevention and SUD treatment, such as homophobia, biphobia, and transphobia; spiritual conflict regarding sexuality; HIV stigma; and medical mistrust. These factors that been found in our previous studies and in the literature to be important predictors of uptake of PrEP; HIV, STI, and HCV screening; and SUD retention [24-28]. Participants assigned to the intervention arm will view photos of, and short introductions to, each of the available peer

mentors; they will then select the peer mentor with whom they anticipate the greatest level of comfort and support based on the photo and introduction. They may also select a backup peer mentor, in case circumstances make a given one unavailable. The selected peer mentor will receive a copy of the participant's passport and their contact information from the project director or research associate and will discuss with them the participant's major issues and strengths.

Peer mentors will meet with their participants approximately every 1-2 weeks for the first 8 weeks to provide support and guidance and to work with them to address barriers in accessing services listed in their passport. Their initial focus will be in ensuring postrelease stability and linkage to services. They will also accompany them to key appointments, assist them in addressing other issues, and encourage productive communication with providers. Furthermore, the peer mentors will engage participants in ongoing evaluation of progress toward their goals and in considering new goals and passport modifications. Peer mentors will be trained to utilize motivational interviewing techniques to help participants resolve ambivalence that might undermine adherence to their services plan outlined in their passport.

In the third and fourth months of the intervention, peer mentors will interact with their participants less frequently than they had during the first 2 months. They will focus more on PrEP engagement and maintenance, HIV and STI screening, and addressing midterm and longer-term goals. During the final 2 months, the peer mentors will begin working with the participants to strategize for a successful transition from peer mentorship and incentives. This will include identifying other external motivators as well as internal motivators for engaging in prevention-related services and behaviors and, if appropriate, encouraging participants to actively identify and engage members of their social network as supports in ongoing maintenance of their health-related goals. Ensuring this smooth transition will be a key focus of the last month of engagement and will be emphasized at the final in-person meeting. All participants completing the final session and at least nine of their 14 scheduled sessions will receive printed certificates of completion.

GeoPass

GeoPass was developed by a MEPS coinvestigator (SM) who is affiliated with Charles R Drew University. It was designed from scratch using Java for Android devices, using Swift for iOS devices, and using ASP.NET for mobile web apps. The participating institutions are listed in the *About the App* section within GeoPass, including the logos of each organization. The app went into production in November 2019, at the start of recruitment; version 1.2 incorporated a geosensing feature update and version 1.3 incorporated geofencing feature additions for all providers.

Intervention participants will download GeoPass and receive their own log-in credentials. The app is downloadable from the Apple Store or Google Play free of charge and is only usable by study participants who are registered by the study team. In the first encounter with their peer mentor, participants will be oriented to the app and its features and encouraged to use it at least once per week. In general, the app is not meant as a stand-alone feature but a tool to facilitate the partnership between the participant and the peer mentor.

The app will create a mobile *passport* that incorporates personalized participant goals with other features that facilitate and motivate the accessing of needed services. These features include reminders, access details for service providers, positive automated feedback when services are utilized and goals attained, and messages from the peer mentors. GeoPass will require participants to provide feedback on services accessed in order to obtain the associated cash incentives. The cash will be transferred to the participant's reloadable bank card. The feedback will involve closed-ended responses to four short questions and the opportunity to enter narrative feedback. Geolocation will validate service utilization using the smartphone's built-in GPS capability and will ping participants to complete the feedback surveys when they attend providers or agencies that are part of an extensive database of local providers compiled for this purpose.

GeoPass will allow peer mentors to view the data for their participants so that they can tailor the subsequent guidance and support that they offer them. Peer mentors will receive push notifications and be able to follow up with their participants in real time via a dashboard that they can access via a peer mentor portal in the app. Geolocation data collection is triggered based on matches to the database of Los Angeles area service providers developed for the study. This database is built and maintained by study staff.

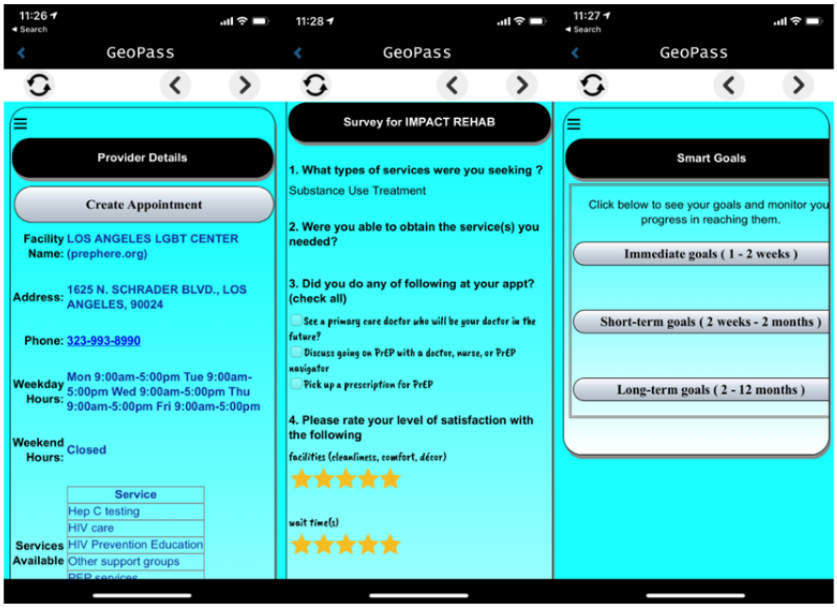
We intend to monitor the following indicators of app use:

1. Number of messages between each peer mentor and participant.
2. Number of surveys completed.
3. Percentage of surveys completed.
4. Number of goals added at baseline and over time.

The use of stored geolocation data will enable us to address secondary aim #3 by describing the temporal and geographic distribution of PrEP uptake and supportive social service utilization patterns of a postincarcerated jail population at high risk for HIV.

Quality assurance for GeoPass incorporated multiple elements. A project consultant acted as a quality assurance specialist and wrote automated tests while the developer was writing code. Four different automated tests were used: (1) static code analysis using Lint and Sonar, (2) executing unit tests to validate whether each unit of the software performed as designed, (3) executing user interface integration tests to ensure that app components were correctly integrated, and (4) virtual device testing to find crashes in Android apps. Every piece of code written by one developer was approved by both Google Play and the Apple Store, and manual testing of the app was done based on specific use cases created by the project consultant acting as quality assurance specialist. Figure 2 displays screenshots taken from GeoPass as they appear on a smartphone.

Figure 2. Screenshots of the GeoPass app.



Incentives

Over the course of the study, intervention arm participants may earn up to US $500 total in reloadable bank card incentives for completing passport activities. Most of these activities will take place over 6 months and are each valued at US $5-$15. These include medically related visits (ie, HIV, STI, and HCV screening and PrEP evaluation), substance use treatment appointments, in-person meetings with their assigned peer mentor or case manager, and nonmedically related items on their passports (eg, support group meetings for gay or bisexual individuals, MSM, or transgender women or training sessions at an employment service center). Certain categories of passport activities, such as substance abuse treatment services and *other*, are expressed as a range because they will vary from participant to participant; they will be determined individually in consultation with the peer mentor, participant, and the participant's case manager, as applicable. A full schedule of different types of activities and the amount of accompanying incentives is provided in Table 1.

The passport's incentive structure is designed to provide more compensation for those study components that are directly related to HIV and STI biomedical intervention or prevention; however, the largest portion of incentives is for SUD services that people with SUDs are recommended to access much more frequently. Frequency for HIV screening (every 3 months), STI screening (every 6 months), and HCV screening (at least once) is based on the Centers for Disease Control and Prevention recommendations for MSM at increased risk for HIV [26]. For the SUD-related services, participants will only be compensated for the number of visits recommended per their ASAM level of care. In addition, the incentives are intended to encourage initial linkage visits to other needed services and are then capped in order to avoid a situation in which participants repeatedly complete incentivized activities after they are no longer beneficial. Once participants take part in a particular service, resolve barriers to service access with a peer mentor, and identify providers they like, it is hoped that they will continue to engage with those services, as needed, regardless of the opportunity for an incentive.

Table 1. Incentive schedule.

Passport activity	Maximum number of times the activity can be completed	Amount, $
Link to a primary care provider who will prescribe PrEP[a]	1	15
PrEP screening and evaluation	1	15
Begin PrEP	1	15
Hepatitis C virus test	1	15
Sexually transmitted infection tests	2	15
HIV tests	3	15
Substance abuse treatment services, including AA[b] and NA[c] meetings, or meetings with case managers	8-14[d]	10
Meetings with peer mentors	14	5 or 15
Other (eg, visits to DPSS[e], job training programs, and counseling)	6-10[d]	15

[a]PrEP: pre-exposure prophylaxis.

[b]AA: Alcoholics Anonymous.

[c]NA: Narcotics Anonymous.

[d]This is expressed as a range because activities will vary from participant to participant and because there is a cap on the total possible compensation.

[e]DPSS: Department of Public Social Services.

Follow-Up Assessments

At 3, 6, and 9 months following the beginning of the intervention, participants will be asked to participate in follow-up interviews to examine changes in behaviors and rates of service utilization; snacks will be provided. Those who are released and then reincarcerated at the scheduled times for their follow-up interviews will be interviewed in custody in the same settings and using the same procedures as described for the baseline interviews that are conducted in custody.

Compensation for Study-Related Activities

For participants in both arms who are in jail, a small stipend will be placed on the participants' inmate commissary accounts (US $25), in compensation for their completion of the baseline survey and any follow-up surveys completed in custody due to reincarceration. Follow-up interviews conducted in the community will be compensated at the rate of US $50. Those participants who remain in jail for more than 3 months but less than 9 months will undergo a second, shortened version of the baseline survey and will receive an extra US $15 placed in their commissary accounts.

Participants interviewed outside of custody will receive US $25 cash for the baseline survey; they will receive US $50 cash compensation for each follow-up survey to account for the increased transportation and opportunity costs associated with participation postenrollment. Additional compensation will be provided throughout the study period for maintaining contact with the study team. Participants in both study arms will be given US $10 per month for initiating contact with the study team within 48 hours of departing jail or a residential facility and providing their up-to-date contact information during each subsequent month through month 9 of follow-up. All participants will receive a *Welcome Home Kit* containing personal items, such as condoms, a battery pack for their phone, and hygiene items of their choosing, worth approximately US $15 in retail value.

Enrolled participants may have an opportunity to refer other individuals for enrollment, for which they can receive bonuses of up to US $75 for 3 enrolled participants.

Outcome and Statistical Data Analysis

Modeling Outcomes

Each outcome will be analyzed via intention-to-treat longitudinal analyses of all available data from the baseline and 3-, 6-, and 9-month follow-up interviews; the mobile app; and the abstracted record data on utilization, as appropriate. Weiss [29] describes our general approach to modeling longitudinal data. For PrEP cascade outcomes, the model is a logistic generalized linear mixed model (GLMM) with a random intercept for participants and a binary 0-1 outcome, with 1 indicating success (eg, screening for PrEP) and 0 indicating a lack of success (eg, not screening for PrEP). The first hypothesis is a test for each outcome of differences at 6 months; secondary hypotheses are tests of differences at 3 months and at 9 months. At baseline, groups have not been affected by interventions; thus, all groups will be the same. Subgroup analyses will be conducted to understand how the intervention outcomes differ by groups. A GLMM random intercept model can be fit in the SAS software PROC MIXED (SAS Institute Inc); if there are problems fitting the data in PROC MIXED, we will move to Bayesian software, such as JAGS in R (The R Foundation) [30].

To analyze visit counts, we will use a Poisson GLMM with log link and an offset equal to the log of the time covered by each observation, with a mean intensity (ie, mean count) of health care visits per unit time. The advantage of this over binary logit GLMM modeling, with 1 (*yes*) being equal to having had at least one visit in the past 3 months versus 0 (*no*) being equal to having no visits in the past 3 months, is that the binary model

penalizes or rewards participants inappropriately for going a few days longer or shorter than 90 days in between visits; in addition, the logit model does not accommodate unbalanced follow-up times.

Modeling Issues and Sensitivity Analyses

Sensitivity analyses will include predictors that are predictive of missing visits or whose average levels differ across study arms. Predictors predictive of missingness are likely to occur; satisfactory randomization should prevent average predictor levels from differing across intervention groups. We will analyze missing visits as a binary outcome with a logistic random intercept regression model. Predictors will be baseline demographics and behavior variables. Examples of predictors are as follows: whether the participant had tested for HIV in the 3 months prior to baseline, age <30 years versus ≥30 years, type of SUD, ASAM Levels I and II versus Levels III and IV, stimulant user versus not, race and ethnicity, preferred substance, and education level.

Variables that are significant predictors of missing visits will be included as predictors in sensitivity analyses of intervention effects. If substantial missingness occurs in key baseline predictors, we will use multiple imputation to fill in the missing predictors. The missing visit analysis omits the baseline time point, as the baseline observation is required. To evaluate randomization, we analyze the key baseline predictors as outcomes in a one-way analysis of variance. If some of the predictors differ by intervention arm, they will be included in sensitivity analyses.

Power Calculations

We aim to enroll 300 total participants in the study, 150 in each group. With this sample size, and allowing for 20% dropout, we can detect a difference between the two groups of 18% (eg, 41% versus 59%) with .80 power at 2-sided α=.05. For rare events, such as initiation of PrEP, we can detect a difference of 14% between the control and intervention groups. We expect a fair amount of loss to follow-up, so we also calculated power for 25% attrition, leaving 112 participants per group.

Multiple Comparisons

We have listed 11 primary outcomes at 6 months for the three specific aims. To adjust for multiple comparisons, we propose to use a new methodology proposed by Harwood et al [31]. For 11 primary outcomes, we expect to reject, on average, 0.55 (ie, 11 × 0.05) null hypotheses, even in the case of no difference between arms. The Harwood et al methodology uses a correlated Bernoulli test of H_0: P=.05 for 11 outcomes that reject the null hypothesis of no effect when 3 or more of the 11 tests are significant at P=.05. Rejecting this null hypothesis means that the interventions are not the same, gives a type I error of .05, and accommodates correlations across outcomes. We then declare individual outcomes that produced a P value below .05 as significantly different across arms as well. We will separately test outcomes at 3 months, 6 months, and 9 months using this methodology.

Participant Safety

The principal investigator and the research team will make every effort to ensure the safety of participants and others throughout the duration of the study. A distress protocol was developed to guide study staff in situations where a participant indicates a desire or plan to harm himself or herself. In the community, peer mentors will also be equipped with emergency referrals to provide where necessary and possible, for resources such as emergency food, housing, domestic violence, and medical and psychiatric care.

Ethics Committee Approval

This study was approved by the Institutional Review Board at the University of California, Los Angeles (UCLA), as well as the LAC Department of Health Services. The study has been registered with ClinicalTrials.gov (NCT04036396).

Results

Recruitment began in November 2019 and will run through April 2022. Findings will be disseminated starting in January 2022 until March 2023, with the final report submitted in March 2023.

Discussion

The MEPS study will address several important gaps in the literature:

1. The study will determine the effectiveness of peer navigation services for biomedical HIV prevention; SUD treatment; and HIV, STI, and HCV screening among MSM and transgender women with SUDs leaving incarceration.
2. The study will examine the acceptability and feasibility of combining peer mentor services with a mobile app to facilitate service utilization and participant-peer communication. To our knowledge, no other study combines these interventions.
3. The study will assess patterns of PrEP uptake and utilization in MSM and transgender women leaving jail, data that are critical to local jurisdictions' abilities to reach goals for the reduction of new HIV infections.
4. Finally, the study will provide heretofore unavailable data on postincarcerated persons' HIV and STI screening, PrEP use, substance use treatment, and service utilization patterns and experiences during re-entry, including geocoded data for those in the two intervention arms. These data may inform resource allocation and strategic planning by policy makers, planners, and other stakeholders.

Peer navigation and peer support have been shown to be acceptable, effective, and cost-efficient strategies for reaching HIV-positive and -negative MSM and transgender women to promote HIV prevention, HIV testing, linkage to HIV primary care, retention in primary care, and viral suppression [32]. However, the efficacy of their use with HIV-negative people leaving jail has not been established. A recent study by Nyamathi et al that compared varying levels of peer coach and nurse-partnered interventions on re-arrests showed no differences from usual care in rates of re-arrest among men on

parole who were recruited from in-patient substance abuse treatment centers [33]. However, their nurse case-management model has shown evidence of effectiveness for improvements in hepatitis A and B vaccine uptake and decreased substance use [27,34]. Expanding the evidence base of effective peer-based approaches is particularly critical now that California and other states are expanding Medicaid reimbursements to cover peer and patient navigation, creating equitable reimbursement rates for substance abuse treatment, and expanding treatment programs to within jails and prisons [35].

The Linking Inmates to Care in Los Angeles (LINK LA) study enrolled 356 HIV-positive people from an MSM and transgender women's jail unit into an RCT comparing a manualized peer mentor intervention to standard transitional case management (TCM). Adjusted probabilities of viral suppression remained stable in the intervention group, from 0.488 at baseline to 0.485 at 12 months; in the TCM group, it declined from 0.520 at baseline to 0.300 at 12 months (P=.002). The Passport to Wellness study has enrolled 92 eligible African American MSM to date in an RCT comparing those assigned to receive a passport, or personalized set of referrals with accompanying incentives for utilization, and the support of a trained peer mentor to those only receiving the passport and incentives. Both groups saw substantial increases in HIV testing, and new enrollment in PrEP increased more for the intervention group than the control group. However, data are very preliminary as, to date, follow-up has not been completed. The proposed study will incorporate elements of both the LINK LA and Passport to Wellness interventions and will enhance them further with the development of GeoPass, which is designed to enhance peer-based interventions and facilitate the use of services along the HIV prevention continuum.

Mobile technology use has become ubiquitous. It is something that individuals of all ages, sexualities, gender statuses, socioeconomic positions, and races and ethnicities regularly utilize in multiple aspects of their daily lives, because it facilitates and enables interactions with information, individuals, businesses, and providers. Service providers can move *one step ahead* by finding efficient and feasible ways to engage these technologies with their participants. To reach marginalized and stigmatized populations who bear a disproportionate share of risk for HIV and other STIs, new initiatives to address HIV prevention must efficiently merge approaches that marshal existing and emerging mobile technologies with those involving more intensive, direct human contact. By enabling researchers and providers the ability to track and provide feedback on participants' service utilization, and by facilitating real-time interaction between participants and peer mentors, web-based mobile technology has the potential to increase utilization and contribute to improved care delivery along the HIV prevention and substance use treatment continua.

Acknowledgments

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Conflicts of Interest

SM is part of the study team and is the lead app developer.

Multimedia Appendix 1
Sample Mobile-Enhanced Prevention Support (MEPS) wellness passport.
[PNG File , 44 KB - resprot_v9i9e18106_app1.png]

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Abbreviations

ASAM: American Society of Addiction Medicine
CHIPTS: Center for HIV Identification, Prevention, and Treatment Services
CHRP: California HIV/AIDS Research Program
CTSI: Center for Translational Sciences Institute
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
GLMM: generalized linear mixed model
HCV: hepatitis C virus
K6G: Keep Away Designation 6G
LAC: Los Angeles County
LA CADA: Los Angeles Centers for Alcohol and Drug Abuse
LASD: Los Angeles County Sheriff's Department
LINK LA: Linking Inmates to Care in Los Angeles
Medi-Cal: Medicaid in California
MEPS: Mobile-Enhanced Prevention Support
MSM: men who have sex with men
NIMH: National Institute of Mental Health
NIMHD: National Institute on Minority Health and Health Disparities
PrEP: pre-exposure prophylaxis
RCT: randomized controlled trial
SCT: Social Cognitive Theory
START: Substance Treatment And Re-entry Transition
STI: sexually transmitted infection
SUD: substance use disorder
TCM: transitional case management

UCLA: University of California, Los Angeles

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Protocol

Optimizing an Acceptance and Commitment Therapy Microintervention Via a Mobile App With Two Cohorts: Protocol for Micro-Randomized Trials

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Abstract

Background: Given gaps in the treatment of mental health, brief adaptive interventions have become a public health imperative. Transdiagnostic interventions may be particularly appropriate given high rates of medical comorbidity and the broader reach of transdiagnostic therapies. One such approach utilized herein is acceptance and commitment therapy (ACT), which is focused on increasing engagement with values, awareness, and openness to internal experiences. ACT theory posits that experiential avoidance is at the center of human suffering, regardless of diagnosis, and, as such, seeks to reduce unworkable experiential avoidance.

Objective: Our objective is to provide the rationale and protocol for examining the safety, feasibility, and effectiveness of optimizing an ACT-based intervention via a mobile app among two disparate samples, which differ in sociodemographic characteristics and symptom profiles.

Methods: Twice each day, participants are prompted via a mobile app to complete assessments of mood and activity and are then randomly assigned to an ACT-based intervention or not. These interventions are questions regarding engagement with values, awareness, and openness to internal experiences. Participant responses are recorded. Analyses will examine completion of assessments, change in symptoms from baseline assessment, and proximal change in mood and activity. A primary outcome of interest is proximal change in activity (eg, form and function of behavior and energy consumed by avoidance and values-based behavior) following interventions as a function of time, symptoms, and behavior, where we hypothesize that participants will focus more energy on values-based behaviors. Analyses will be conducted using a weighted and centered least squares approach. Two samples will run concurrently to assess the capacity of optimizing mobile ACT in populations that differ widely in their clinical presentation and sociodemographic characteristics: individuals with bipolar disorder (n=30) and distressed first-generation college students (n=50).

Results: Recruitment began on September 10, 2019, for the bipolar sample and on October 5, 2019, for the college sample. Participation in the study began on October 18, 2019.

Conclusions: This study examines an ACT-based intervention among two disparate samples. Should ACT demonstrate feasibility and preliminary effectiveness in each sample, a large randomized controlled trial applying ACT across diagnoses and demographics would be indicated. The public health implications of such an approach may be far-reaching.

Trial Registration: ClinicalTrials.gov NCT04098497; https://clinicaltrials.gov/ct2/show/NCT04098497; ClinicalTrials.gov NCT04081662; https://clinicaltrials.gov/ct2/show/NCT04081662

International Registered Report Identifier (IRRID): DERR1-10.2196/17086

(JMIR Res Protoc 2020;9(9):e17086) doi:10.2196/17086

KEYWORDS

acceptance and commitment therapy; clinical trial; mobile apps; bipolar disorder; students; mobile phone

Introduction

Background

Brief interventions have garnered public health attention in recent years regarding improvements in patient and provider efficiency. Many studies have indicated the effectiveness of brief interventions in creating and sustaining clinically meaningful levels of change. Several meta-analyses [1,2] and large community-based studies [3] indicate that rapid improvements in symptoms often occur after brief interventions and that change occurs at an accelerated rate when patients are provided fewer therapy sessions [4]. Wide-scale applications of effective brief approaches that reach diverse patient groups, particularly those with limited access to services, are important.

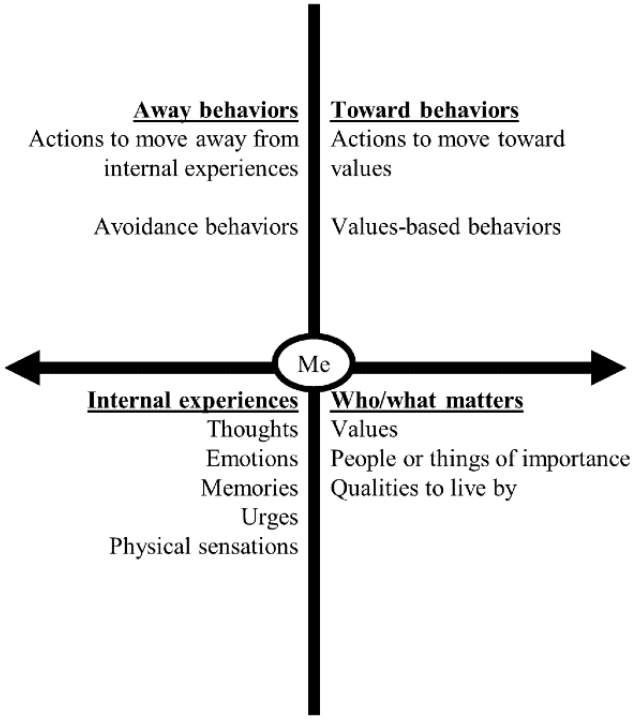
Digitally delivered interventions are promising in terms of reach, acceptability, individualization, and cost-effectiveness. Users can tailor consumption of content, seeking support when needed, and integration with the users' context can be provided. Despite great potential and expanded capacity, many digital interventions have yet to be evaluated for effectiveness in randomized controlled trials (RCTs) [5]. Moreover, digital interventions are frequently developed for a specific mental health disorder, such as bipolar disorder [6], borderline personality disorder [7], major depressive disorder [8], anxiety disorders [9], and posttraumatic stress disorder [10]. Naturally, digital interventions that are effective across affective disorders have potential for helping a greater number of individuals. By developing a brief, digitally delivered intervention, the goal of this study is to identify whether a transdiagnostic approach could be adapted to a microintervention design, exploring the proximal impacts of interventions on mood and activity. The implications of a brief, effective, and easily disseminated mobile app are far-reaching, given large treatment gaps in mental health [11]. Furthermore, transdiagnostic interventions that target functioning over symptoms have broad potential to impact human suffering across diagnostic presentations and comorbidities. Acceptance and commitment therapy (ACT) is a transdiagnostic, process-based intervention that has established empirical support in over 300 RCTs. This manuscript presents two parallel protocols for micro-randomized trials for optimizing an ACT-based mobile app in two samples with pronounced differences in sociodemographic backgrounds and in symptom profiles: (1) individuals with bipolar disorder and (2) distressed first-generation college students.

ACT

ACT is a transdiagnostic, mindfulness-based, and acceptance-based behavioral therapy. Its overarching goal is to increase psychological flexibility, allowing patients to behave consistently with their values, even in the presence of difficult thoughts, emotions, or other internal experiences [12]. Psychological flexibility includes awareness of internal experiences (eg, thoughts and emotions) and behaviors, openness to internal experiences, and engagement with values. Notably, the central goal of ACT is not to remove unwanted symptoms (eg, distress and depression) but to help individuals pursue a life of meaning even in the presence of such symptoms. ACT targets experiential avoidance: the inability or unwillingness to make contact with internal experiences (eg, thoughts, emotions, and memories) [12]. Avoidance provides short-term relief but exacerbates long-term experiences of the avoided stimulus in intensity and duration. Avoidance also reduces contact with valued life directions. Conversely, psychological flexibility is associated with increased well-being and reduced symptoms [13].

ACT has demonstrated efficacy when delivered to transdiagnostic populations and over brief periods (eg, a few weeks or digitally) [14-16]. ACT effectively treats a number of psychiatric and physical conditions, including chronic pain, depression, and anxiety [13]. For example, ACT has improved depressive symptoms in a sample of college students via an online, guided intervention [17]. An ACT-based mobile app improved psychological flexibility [18], suggesting that improvements can be achieved utilizing mobile technology [19-22]. By synthesizing processes related to ACT, the ACT matrix helps patients to identify values, values-based behaviors, internal experiences, and avoidance behaviors (see Figure 1) [23]. This tool has been utilized in brief RCTs demonstrating positive outcomes [24,25]. Despite support for ACT in brief form and via digital media, research has not yet examined microinterventions related to specific ACT processes (ie, openness, awareness, and engagement, as discussed below). Furthermore, in development of such an intervention, it is important to know whether such an approach would work *across* samples of differing backgrounds and diagnostic presentations, as would be hypothesized with a transdiagnostic approach.

Figure 1. The acceptance and commitment therapy (ACT) matrix. The ACT matrix encourages awareness of one's values, internal experiences, and the function of one's behaviors. The top two quadrants are observable behaviors, while the bottom two quadrants are internal experiences and not observable to others. The middle circle signifies the ability to notice each of these domains, categorizing all quadrants as part of a person's experience.



Micro-Randomized Trials

Micro-randomized trials are a new type of RCT well suited for optimizing interventions delivered via mobile apps [26,27]. In a traditional RCT, individuals are randomized once to an intervention condition. Researchers can then estimate causal effects of the intervention on outcomes. In contrast, micro-randomized trials repeatedly randomize individuals to intervention groups, and causal effects of the interventions on proximal outcomes can be estimated in a micro-randomized trial. Because randomization is repeated, the moderating role of in-the-moment information (eg, current symptoms) on causal effects of the intervention can be examined. With many mobile interventions striving to intervene *just-in-time* [28], micro-randomized trials can provide evidence on what immediate information is needed to optimize the timing of psychosocial interventions. Micro-randomized trials have evaluated physical health and substance use interventions [29-31], but they have not evaluated such interventions among bipolar individuals or distressed college students, or ones based on ACT.

Objective

The micro-randomized trials in this study evaluate safety, feasibility, and effectiveness of optimizing an ACT-based microintervention via a mobile app over the course of 6 weeks. To investigate the possibility of optimizing mobile ACT in transdiagnostic populations, two samples with clinically distinct presentations are studied: (1) distressed first-generation college students and (2) individuals with bipolar disorder. As detailed in the Methods section below, these samples differ noticeably in the severity and chronicity of affective illness, affective symptoms manifestation, and sociodemographic characteristics. The two trials seek to examine the proximal effects of the intervention across the samples in terms of mood, perceived stress, and/or activity. The overarching goal of the trials is to determine whether optimizing an ACT-based app has potential to help with behavioral and mood changes in diverse and transdiagnostic populations. The findings bear on improving access to care, providing adjuncts to traditional psychotherapy, and increasing efficiency in delivery of psychotherapy.

Methods

Study Design

The two studies described in this paper share one core research design, adapted to fit each cohort. Each study uses a micro-randomized trial to evaluate safety, feasibility, and effectiveness of a mobile ACT-based intervention. This intervention consists of prompts designed to embody the central tenets of ACT. The intervention is delivered over 6 weeks through an app designed for these studies. Because the scale of delivery is small compared to a traditional intervention, we refer to this as a *microintervention.* Both studies were registered at ClinicalTrials.gov (NCT04098497 and NCT04081662).

After consenting, participants complete baseline questionnaires on symptoms, functioning, and background information. Participants are prompted to download a mobile app designed for the study. Upon opening the app, participants are provided the link and encouraged to watch a 20-minute video that introduces the core concepts of the intervention. Participants are asked to log symptoms in the app. Each time the participant logs symptoms, they have a 50% chance of receiving a microintervention, which is randomly chosen from a set of 84 questions. Participants answer questions about the activities they are currently engaged in. They are asked to identify the form of the activity (eg, walking dog) as well as the function

of the behavior (ie, toward values or away from internal experiences). After the conclusion of the 6-week study, participants complete follow-up symptom scales and questionnaires.

Table 1 summarizes the study design and differences between each cohort. The difference between cohorts is the set of symptom scales used at baseline, follow-up, and in the app. For individuals with bipolar disorder, scales measure mania and depression. For distressed first-generation students, scales measure stress and depression. Sample-specific scale selection affords an opportunity to observe the relevant symptoms and to evaluate effectiveness of the microintervention in alleviating symptoms. See Table 1 [32-39] for the complete assessment battery.

Table 1. Summary of study design and differences between cohorts.

Design element	Bipolar cohort	College student cohort
Sample size, n	30	50
Baseline assessments (day 0)	A phone interview[a] to complete the YMRS[b] [34], the SIGH-D[c] [35], and the SF-36[d] [36]	An online assessment to complete the PSS-10[e] [32], the PHQ-9[f] [33], the PROMIS-29[g] [37], the AAQ-2[h] [38], and the CompACT[i] [39]
In-app assessments (days 1-42)	Delivered through the app twice daily: the shortened YMRS, the shortened SIGH-D, and the ACT[j] Activity Survey[k]	Delivered through the app twice daily: the PHQ-2[l], the PSS-4[m], and the ACT Activity Survey[k]
Activity tracker assessments (days 1-42)	Sleep, heart rate, and steps tracked through the Fitbit Alta HR	None
Microintervention (days 1-42)	Randomized to receive or not receive ACT microintervention[k] after in-app assessments	Randomized to receive or not receive ACT microintervention[k] after in-app assessments
Exit assessments (day 42)	A phone interview to complete same assessments from baseline	An online assessment to complete same assessments from baseline, along with an app engagement survey[k]
Follow-up assessments (months 3 and 6)	None	Online assessments to complete same assessments from baseline
Primary outcomes	Safety and feasibility of microintervention in terms of the following: adherence to in-app assessments (ie, feasibility); change in YMRS and SIGH-D scores from baseline to exit assessment (ie, safety)	Effectiveness, safety, and feasibility of microintervention in terms of the following: changes in responses to ACT Activity Survey as a function of whether the microintervention was delivered at a prior time point (ie, effectiveness); adherence to in-app assessments (ie, feasibility); change in proportion of individuals who meet criteria for minor or major depression on PHQ-9 from baseline to exit and from baseline to each follow-up assessment (ie, safety)
Secondary outcomes	Power for larger study based on changes in responses to ACT Activity Survey as a function of whether the microintervention was delivered at a prior time point (ie, effectiveness)	Effectiveness of microintervention in terms of changes in responses to PHQ-2 and PSS-4 scores as a function of whether the microintervention was delivered at a prior time point (ie, effectiveness)

[a]Participants are recruited from the Prechter Longitudinal Study of Bipolar Disorder and have already completed interviews to determine demographic information and health and mental illness history.

[b]YMRS: Young Mania Rating Scale.

[c]SIGH-D: Structured Interview Guide for the Hamilton Depression Rating Scale.

[d]SF-36: 36-Item Short Form Survey.

[e]PSS-10: Perceived Stress Scale 10.

[f]PHQ-9: Patient Health Questionnaire 9.

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

[h]AAQ2: Acceptance and Action Questionnaire-II.

[i]CompACT: Comprehensive Assessment of Acceptance and Commitment Therapy Processes.

[j]ACT: acceptance and commitment therapy.

[k]Developed for these studies.

[l]PHQ-2: Patient Health Questionnaire 2.

[m]PSS-4: Perceived Stress Scale 4.

Randomization

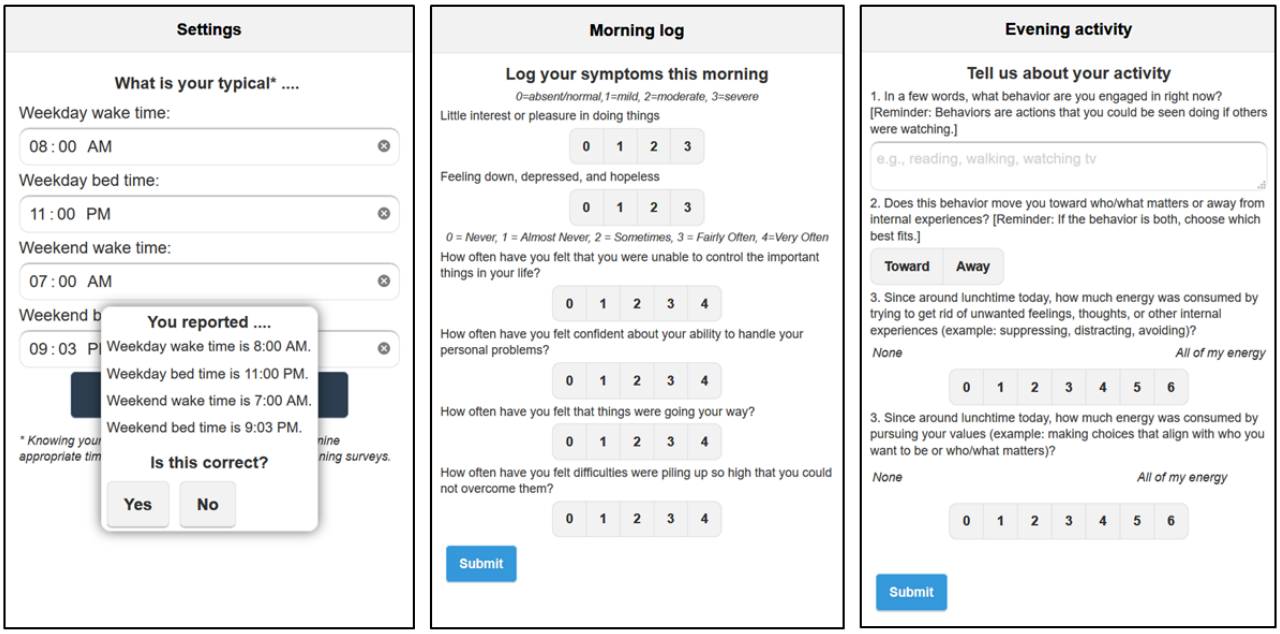
Participants are repeatedly randomized to either receive an intervention or not receive an intervention throughout the study. Participants are *available* for randomization every time they complete an in-app assessment, which can be completed once in the morning and once in the evening throughout the study. Randomization occurs immediately after a participant clicks the button to submit an in-app assessment. Participants have a 50-50 chance of receiving a microintervention. Since there are a total of 84 different assessments (2 per day × 42 days), participants may be randomized to receive a microintervention for a maximum of 84 different times throughout the study. If the participant is not assigned to receive a microintervention, then they are taken to the home page. If they are assigned to receive a microintervention, then a second randomization is performed to determine which of the 84 prompts will be delivered, and the participant is taken to a new screen with this microintervention prompt on the screen. This second randomization is defined such that each microintervention prompt is equally likely of being delivered. We remark that this second randomization means that a small portion of microinterventions (~10%) may be received more than once. An alternative approach would be to randomize without replacement to ensure a microintervention is delivered only once. We opted for the simpler approach of randomization with replacement, since we do not know whether a microintervention is more effective if delivered more than once, by way of reinforcing a behavior or thought, or less effective because of the redundancy.

Mobile App

Overview

The microintervention is delivered by an app called Lorevimo (see Figure 2), originally developed and tested for assessing engagement strategies for digital self-monitoring of symptoms in bipolar disorder [40,41]. The app was adapted to measure relevant symptoms for each cohort, deliver the microintervention, and integrate responses into the ACT matrix. Lorevimo is restricted to participants through a coded username and password provided to them through the study to protect privacy. The app is available for free in Android through Google Play and in iOS through iTunes. The app was developed using third-party software called Appery.io (Exadel, Inc), which combines drag-and-drop functionality with JavaScript to allow for easy development and advanced control. Appery.io also provides back-end functionality for the app (eg, servers, databases, application programming interface integration, and push notifications) and packages apps for Android and iOS. Lorevimo's name is derived from its three functions—*log*, *review*, and *visualize your mood*—which we proceed to detail.

Figure 2. Log functions of the Lorevimo app. The first screen (left) is where participants can set regular weekday and weekend wake times and bedtimes, which determines when they are prompted to log symptoms and activities. The second screen (center) is the mood symptoms log, including depression symptoms and perceived stress. The third screen (right) is the activity questionnaire.



Log

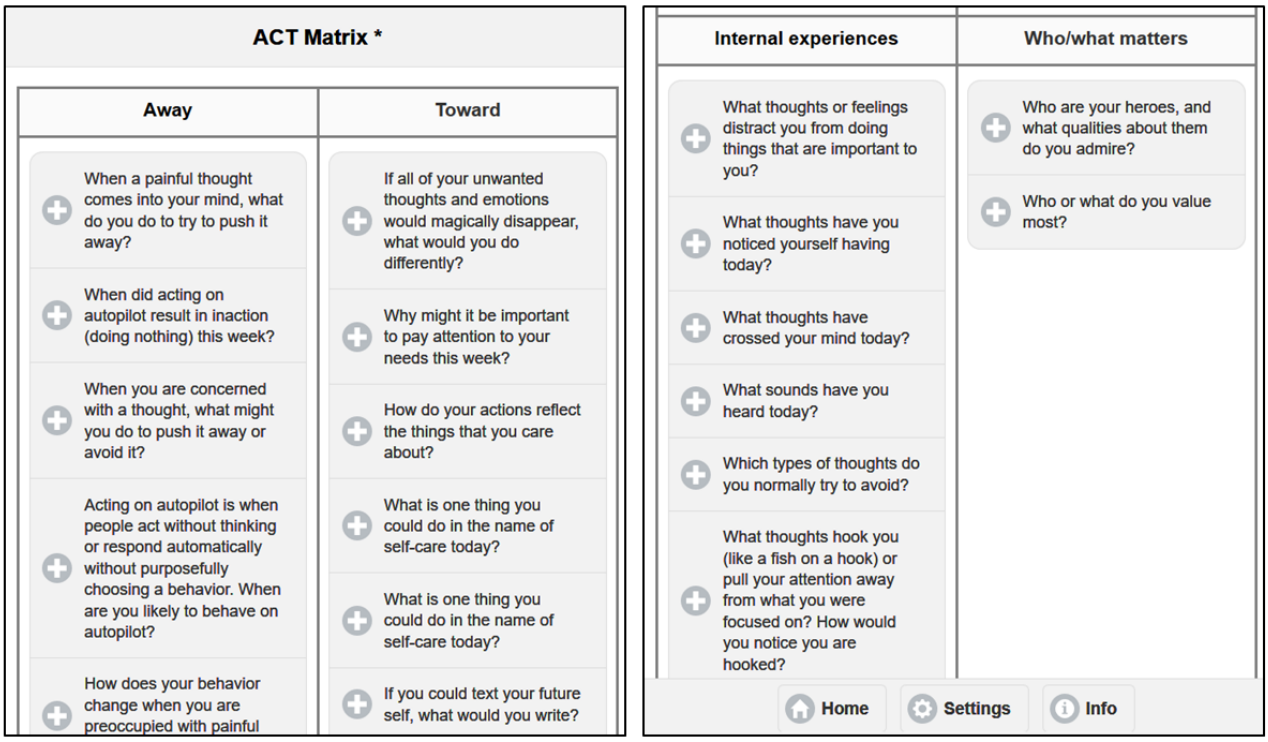
Once in the morning and evening, participants log symptoms upon clicking *Log* from the home page. After logging, the app randomizes participants to the microintervention. The app presents an ACT-based question to participants randomized to the intervention. Morning and evening are defined based on reported typical wake times and bedtimes on weekdays and weekends, reported at first log-in. Times can be changed under *Settings* in the app. Morning is defined as 2-7 hours after typical wake time. Evening is defined as 3 hours before, to 2 hours after, typical bedtime. Push notifications are sent at 2-hour intervals if symptoms have not been logged within the relevant interval and if the notification can be sent before 30 minutes of the typical bedtime.

Review

Upon clicking *Review* (see Figure 3) from the home page, the user views an ACT matrix populated with microintervention-completed prompts and responses, sorted

based on the targeted concept: avoidance behaviors, values-based behaviors, internal experiences, and values.

Figure 3. Review function of the Lorevimo app. The first image (left) represents the top half of the acceptance and commitment therapy (ACT) matrix, which sorts the function of behaviors. The second image (right) represents the bottom half of the ACT matrix, which sorts internal experiences and values (ie, who or what matters).



Visualize

Upon clicking *Visualize* (see Figure 4) from the app's home page, the user is shown a graph of symptoms over the past week. The time interval can be changed (ie, 3, 7, or 28 days). The *Visualize* and *Review* functions were designed to help increase awareness, which is a central tenet of ACT, and encourage individuals to continue to log symptoms.

Figure 4. Visualize function of the Lorevimo app. The images represent screenshots of the Lorevimo app's Visualize function. The first image (left) is a representation of the depressive symptoms in a 3-day (twice daily) interval. The second image (center) conveys the perceived stress symptoms (also a 3-day interval). The final image (right) reflects the responses to the question about energy consumed by avoidance behaviors (ie, away from internal experiences) or values-based behaviors (ie, toward who or what matters).

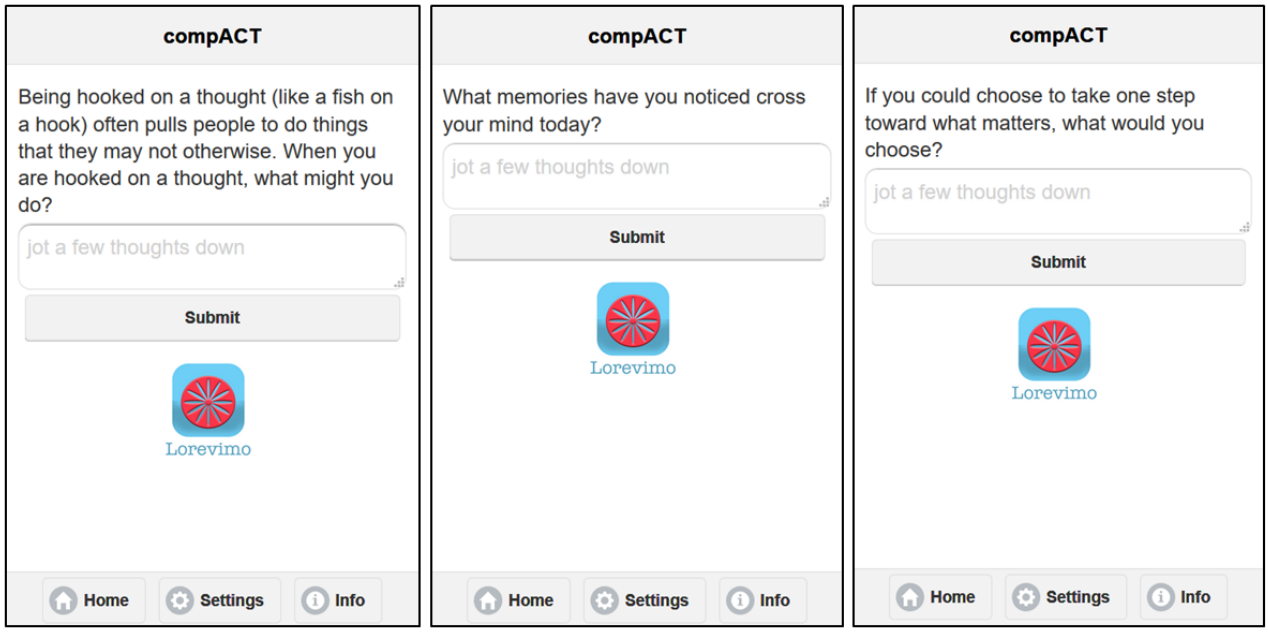
Microintervention

In order to understand the twice-daily assessment questions regarding behavior and the function of behavior, participants must be familiar with how values, behaviors, and internal experiences fit into the framework of ACT. When participants log in to the app for the first time, they are prompted to watch an introductory video. The same introductory video is used in both studies. In the video, two members of the research team role-play a therapist and client. The purpose of the video is to illustrate the ACT matrix (see Figure 1): identifying and sorting values, internal experiences, avoidance behaviors, and values-based behaviors [23]. The team prompts the viewers to create a matrix reflective of their experiences. The video is intended to promote mindful behavioral awareness and to model the noticing and sorting of one's experiences, and participants are explicitly told this. The assessment questions are explained in the video as well: form of behavior, function, and the amount of energy expended in avoidance behaviors and values-based behaviors. Answers to microintervention prompts are also used to populate the ACT matrix in the study app. As answers to microintervention prompts accumulate in the matrix, participants can review (see Figure 3) experiences within the theoretical framework.

Following completion of the assessment, the participants may be randomized to receive an intervention prompt. The microintervention consists of 84 ACT-based questions developed by the research team. The questions are intended to be small-scale opportunities to build ACT skills, including openness to internal experiences via acceptance and defusion; awareness via mindfulness, self-as-context, and perspective taking; and engagement via values clarification and committed action. These questions can be organized into three subcategories (28 questions per subcategory), each corresponding to a core concept of ACT:

1. Openness to internal experiences and willingness to feel emotions in service of values (see Figure 5, left).
2. Awareness of one's internal experiences (eg, thoughts, emotions, memories, urges, and physical sensations) and external context, as well as awareness of being present and in the moment rather than acting on autopilot (see Figure 5, center).
3. Engagement with values (ie, important people, important areas of life or things, and qualities one wishes to embody) (see Figure 5, right).

Figure 5. Microintervention examples from the Lorevimo app. These images reflect three of the 84 acceptance and commitment therapy (ACT)-based intervention questions, also allowing space for participants to enter a response. The first (left) is an *openness* question, the second (center) an *awareness* question, and the third (right) an *engagement* question. CompACT: Comprehensive Assessment of Acceptance and Commitment Therapy Processes.



The questions are designed to encourage participants to be intentional in action and mindful of thoughts and emotions. The openness subcategory encourages participants to accept internal experiences—positive or negative—rather than engaging in avoidance to suppress or attempt to be rid of such experiences. Awareness questions encourage participants to pay attention on purpose, engaging in mindfulness and intentional presence. Finally, engagement questions prompt participants to consider values: people, things, and qualities of being that are important. In addition, engagement prompts participants to examine the consistency between identified values and current behavior, and to help participants align current behavior with values.

Study 1: Distressed First-Generation College Students

Motivation

The transition to college is associated with changes in health behaviors and mental health functioning, with 50% of college students meeting criteria for a psychiatric disorder [42]. First-generation college students may be at elevated risk for stress and mental health difficulties [43]. The development of adaptive interventions may help provide adequate and accessible care during these dynamic, transitional years. Delivery of these interventions via acceptable and feasible modalities for this

population is of utmost importance so that utilization and engagement are prioritized.

This investigation seeks to integrate provision of psychotherapy skills, daily assessment of symptoms and activities, and digital delivery of interventions in a sample of distressed first-generation college students. Given that college students are often required to utilize technology in the classroom, as well as potentially in other settings (eg, using public transportation on campus), the development of an app aimed to reduce distress and increase values-based behaviors may have wide-ranging impact on the well-being of college students, while also integrating into a familiar digital context.

Participants

A total of 50 students will be recruited from the University of Wisconsin–Madison to participant in a 6-week study focusing on effectiveness, safety, and feasibility of the microintervention. This study has been approved by the Health Sciences Institutional Review Board at the University of Wisconsin–Madison (2019-0819). Inclusion criteria, which will be determined from a screening instrument, are that participants must (1) be currently enrolled freshman or sophomore students at the University of Wisconsin–Madison, (2) be first-generation college students (ie, neither parent or legal guardian of the student holds a bachelor's degree or above), (3) endorse functional impairment by distress at the time of screening, defined as experiencing impairment in one or more domains on at least 4 out of the past 7 days, and (4) have a smartphone. There were no exclusion criteria. Participation is open to all gender identities, adults aged 18 and 19 years, and all ethnic and racial groups. A consent discussion will occur by phone, followed by electronic submission of signed consent through Research Electronic Data Capture (REDCap) (Vanderbilt University). A PDF of the informed consent document will be provided for participants' records via email. Recruitment began in fall 2019. Recruitment methods will include mass email, posting flyers on the University of Wisconsin–Madison campus, and brief presentations during University of Wisconsin–Madison classes. Subject recruitment and enrollment will occur over 18 months with the total duration of the trial expected to be 30 months, including the microintervention and follow-up data collection.

Remuneration

Participants are remunerated for both research and intervention activities. Participants are remunerated for each week in which they complete at least 50% of daily in-app assessments throughout the 6-week intervention period, as well as for completion of baseline and follow-up assessments. A bonus will be provided to participants who complete all 6 weeks of the intervention period.

Assessments

Assessments measure stress and depression. Participants are assessed in REDCap at baseline, exit, 3-month follow-up, and 6-month follow-up with the Perceived Stress Scale 10 (PSS-10) [32] and the Patient Health Questionnaire 9 (PHQ-9) [33]. The Patient Health Questionnaire 2 (PHQ-2) consists of the first two items from the PHQ-9, measuring the two gatekeeper symptoms of depression: dysphoria and anhedonia. Twice-daily in-app assessments include the Perceived Stress Scale 4 (PSS-4) [44], the PHQ-2, and the ACT Activity Survey.

Outcomes

Primary outcomes for the college student cohort measure effectiveness, feasibility, and safety of the microintervention (see Table 1):

1. Effectiveness. Because the microintervention is delivered immediately after an assessment, outcomes to assess effectiveness are based on the very next assessment. That is, if the intervention is provided in the morning, then its effect is measured on assessments in the evening. Responses are called *proximal outcomes* for their proximity to the intervention. Proximal outcomes of interest are primarily responses to the last two questions on an ACT Activity Survey, but we will also consider scores on symptom scales (ie, PHQ-2 and PSS-4).
2. Feasibility. One potential barrier for a micro-randomized trial is insufficient proximal outcome data for measuring effectiveness. Given proximal outcomes are recovered from in-app assessments, then feasibility outcomes include adherence to in-app assessments (ie, completion of at least 50% of daily items). A similar 50% benchmark was used in our preceding study [40,41]. Participants can respond to 20 items each day ([6 symptom items + 4 activity items] × 2 per day). Additional outcomes include quality of engagement with the ACT microintervention (ie, number of words in responses and relevance of content).
3. Safety. While safety outcomes are often related to adverse events, given an expected minimal risk of this study, we focused on safety outcomes that indicate a worsening of symptoms. Specifically, the proportion of individuals with PHQ-9 scores above 10 between baseline, exit, and follow-up will be examined. These outcomes provide low-level evidence (ie, not causal evidence) that participating in the study worsens mood symptoms.

Power Analyses

For the college student cohort, power was calculated using the supported calculator for adaptive interventions [26], available online [45]. In this case, sample size was calculated to test for a linear effect of time of intervention on proximal outcome measures (ie, depression, stress, and activity). We expect a smaller effect size, on average, than an effect size for an in-person psychotherapy intervention [26]. We expect a small-to-medium effect size (~0.1-0.2) on average. In addition, we hypothesize that participants will respond to 80% of prompts based on a prior study of user engagement that used Lorevimo [41]. Conservatively assuming a linear effect, which on average produces a small or medium effect size of 0.1, and assuming subjects respond 80% of the time, 50 subjects will yield 83.8% power to detect a linear effect with a significance level of .05.

Statistical Analyses

For feasibility, our hypothesis is that participants will adhere to in-app assessments (ie, respond to over half of the assessments per day, for over 60% of the days of the intervention period on average). To test this hypothesis, a one-sample z test of

proportions will be performed to determine whether average percent of days to which a participant adheres to in-app assessments differs significantly from 60%. Given our overarching goal of a micro-randomized trial in a transdiagnostic population, a cutoff of 60% is considered a lower bound for adherence needed to power such a larger study (ie, go or no-go criteria) and is thought to be a meaningful deviation from the 80% adherence from our preceding study. For reference, 117 individuals would be needed if individuals only responded to 30% of prompts (60% of days × half the completion) to achieve the same power as in this study under the same assumptions as above. Our hypothesis related to safety is that the proportion of individuals with a PHQ-9 score of 10 or above between baseline to exit or between baseline to each follow-up will not increase, and a one-sample z test of proportions will be performed to determine whether these proportions are significantly different from zero.

To test effectiveness, we will use a weighted and centered least squares method [29,46] to estimate and test the average effect of delivering a microintervention on each proximal outcome as a function of time in the study conditional on the participant being available for randomization (ie, the participant completed the in-app assessment at the prior time point). Two proximal outcomes will be evaluated: energy devoted to values-based or avoidance behaviors, as measured on our ACT Activity Survey. The treatment effect model will control for an intercept and time and will be linear in the binary intervention variable, centered at the probability of receiving an intervention, and the interaction (ie, time × centered intervention variable). To account for repeated samples and nonindependence, robust standard errors will be calculated using a sandwich estimator [46]. The interaction term will be tested for statistical significance ($P<.05$).

Data may be missing if a participant does not complete an in-app assessment, resulting in missing proximal outcomes. This missingness may introduce estimation bias for average microintervention effects if the microintervention delivery were to influence whether or not the next proximal outcome is missing. If no more than 10% of the data are missing, then our primary analysis would be a complete-case analysis, which assumes that whether or not the proximal outcome is missing is independent from microintervention delivery and includes only data points without a missing proximal outcome in our analysis. Follow-up analysis would then examine the sensitivity of our estimates to this independence assumption in two steps. First, we would identify variables available prior to each randomization that predict whether or not the proximal outcome is missing. Candidate variables include the outcome of interest measured at prior time points, prior number of interventions and assessments, and prior number of missing proximal outcomes and assessments. Second, we would then repeat analyses controlling for these variables in the weighted and centered least squares method. If more than 10% of the data are missing, then the above analysis, which controls for the variables' associated missingness, will be used as our primary analysis, and a complete-case analysis would be used as a follow-up analysis.

Exploratory Analyses

To better optimize the intervention, further exploratory analyses will be performed to determine if the effect of the intervention on proximal outcomes is moderated by momentary information, such as the microintervention subcategory (ie, engagement, openness, or activity) and current symptoms and behavior. Additional exploratory variables of interest include childhood trauma and resilience, measured via self-report.

We will perform a qualitative analysis of microintervention responses to examine comprehension of ACT processes. Two members of the research team (SH and AV), who were trained in identifying and applying the theoretical components of ACT, will code responses for process alignment. Each microintervention prompt targets one of the three core ACT processes described above: openness, awareness, and engagement. The methods for developing codes and results of this analysis will be published at a later date. Coders will also code behavioral responses and the function of behavior. In particular, we are interested in whether behaviors of the same form (eg, exercise) serve different functions throughout the study (eg, avoidance of stress vs pursuit of health). This diversity of function would be indicative of behavioral awareness.

Study 2: Individuals With Bipolar Disorder

Motivation

Bipolar disorder is a chronic mood disorder that affects 2.4% of individuals worldwide [47] and ranks seventh among disability-causing diseases among men and eighth among women [11]. Individuals with bipolar disorder experience profound shifts in mood ranging from depression to mania. Treatment includes medication and/or psychotherapy. However, relapse and nonadherence with medication, along with access to care, remain common barriers to maintaining stability in mood. Consequently, mood may shift dramatically within days, with little advanced warning, and due to unpredictable events [48]. Treatment guidelines are often insufficiently nuanced to predict when, where, and how to intervene. New adaptive strategies are necessary to optimize promising psychotherapies in an effort to make them more accessible and efficient at interpreting individual needs. The current micro-randomized trial based on ACT takes a first step toward investigating effective mobile adaptive interventions for bipolar disorder.

Participants

A total of 30 participants will be recruited from the Prechter Longitudinal Study of Bipolar Disorder [49] to participate in a 6-week study examining the safety and feasibility of the microintervention. The institutional review boards at the University of Michigan (HUM126732) and University of Wisconsin (2017-1322) have approved the study. The study did not include a data safety monitoring board. Inclusion criteria include a diagnosis of bipolar disorder (ie, type I, type II, or not otherwise specified), agreement to be contacted for future research, and access to a smartphone. Participants in the Prechter Longitudinal Study of Bipolar Disorder have completed a Diagnostic Interview for Genetic Studies (DIGS) to collect mental and physical health history, including bipolar disorder diagnosis. Potential participants will be contacted via

recruitment email or phone call. If interested and eligible, participants will consent by phone, and the consent form will be electronically signed through the Health Insurance Portability and Accountability Act (HIPAA)-compliant data capture software REDCap. Adults of all genders and ethnic and racial backgrounds are eligible. Following a preceding study of digital self-monitoring in bipolar disorder [40,41], participants will be mailed an activity tracker: Fitbit Alta HR. The inclusion of a Fitbit would allow us to explore a possible relationship between mobile ACT effectiveness and sleep, activity, and heart rate, which are considered to both indicate and moderate symptoms of mania and depression. Participants will contact the study team upon receipt, and an entrance interview will be completed.

Remuneration

Participants are remunerated based on research activities, defined as the completion of exit and entrance interviews and completion of participation in study weeks 1 through 5. Remuneration is submitted once participants complete the exit interview at the end of the 6 weeks. If a participant ends their participation in the study early, they are to be remunerated based on how many weeks they have completed, and whether or not they completed the exit interview.

Assessments

Assessments for the bipolar cohort focus on manic and depressive symptoms (see Table 1). Participants are assessed over the phone at baseline and exit with the Young Mania Rating Scale (YMRS) [34] and the Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D) [35]. The 36-Item Short Form Survey (SF-36) [36] is administered at these time points to assess general health and well-being. Shortened versions of the YMRS and the SIGH-D are completed via twice-daily in-app assessments. These shortened versions were first introduced in Cochran et al [49] in a study of engagement in digital self-monitoring among individuals with bipolar disorder. While the validation of psychometric properties of these shortened versions is ongoing, they were introduced in an effort to address a need for a digital instrument that is brief but can separately measure severity of manic symptoms and severity of depressive symptoms. The same ACT Activity Survey used in the college sample will be assessed in-app. The ACT Activity Survey consists of four questions that target ACT concepts: (1) What behavior are you engaging in right now? (2) Is this behavior moving you toward who/what matters or away from internal experiences? (3) Since this [morning or lunch time], how much energy was consumed by avoidance? (4) Since this [morning or lunch time], how much energy was consumed by pursuing values? See the assessment in Multimedia Appendix 1.

Outcomes

Primary outcomes for the bipolar cohort measure feasibility and safety of the microintervention (see Table 1). Effectiveness is left as a secondary outcome due to limited power and will be used to determine power for a future study.

1. Feasibility. Following the other sample, outcomes to assess feasibility are adherence to in-app assessments (ie, completion of at least 50% of daily items).
2. Safety. Safety outcomes are average changes in YMRS and SIGH-D scores from baseline to exit, proportion of individuals with increased YMRS scores from baseline to exit, and proportion of individuals with increased SIGH-D scores from baseline to exit. These outcomes provide low-level evidence (ie, not causal evidence) that participating in the study is worsening mood symptoms.
3. Effectiveness (secondary outcome). Proximal outcomes of interest are primarily responses to the last two questions on an ACT Activity Survey, but we will also consider scores on symptom scales (ie, in-app manic and depressive symptom assessments).

Power Analyses

A sample size of 30 subjects would yield 58.6% power to detect a linear effect of microinterventions that is, on average, 0.1 over the study, assuming subjects respond 80% of the time, with a significance level of .05. However, the sample size for the bipolar cohort was not specified to have sufficient power to evaluate effectiveness, since effectiveness of the microintervention is not a primary outcome. The sample size for the bipolar cohort was specified to estimate the intervention effect and adherence to in-app assessments to use as input for powering a larger study.

Statistical Analyses

Our feasibility hypothesis, which is identical to the feasibility hypothesis for the college sample, is that participants will adhere to in-app assessments (ie, respond to over half of the assessments per day, for over 60% of the days of the intervention period on average). To test this hypothesis, a one-sample z test of proportions will be performed to determine whether average percent of days to which a participant adheres to in-app assessments differs significantly from 60%. Our safety hypotheses are that mean YMRS or SIGH-D scores will not decrease from baseline to study exit, an equal proportion of individuals will see an increase in YMRS scores as a decrease from baseline to study exit, and an equal proportion of individuals will see an increase in SIGH-D scores as a decrease from baseline to study exit. A one-sample *t* test will be performed to determine whether changes in mean scores are significantly different from zero, and a rank test will be performed to test for equal proportions. Our effectiveness hypothesis is that the microintervention has an approximate linear effect in time on proximal outcomes of energy devoted to values-based or avoidance behaviors. As for the college sample, the weighted and centered least squares method [29,46] will be used to estimate and test the average effect of delivering a microintervention on each proximal outcome as a function of time in the study, conditional on the participant being available for randomization (ie, the participant completed the in-app assessment at the prior time point). The weighted and centered least squares method will control for the intercept and time and will use a linear treatment effect model with a binary intervention variable, centered at the probability of receiving an intervention, and interaction (ie, time × centered intervention). Robust standard errors will be calculated [46]. The interaction term will be tested for statistical significance (P<.05) to determine if the invention has a linear effect on

proximal outcomes. Missing data for the bipolar sample would be handled in the same way they are handled for the college sample.

Exploratory Analyses

For the bipolar sample, we will also explore whether the effect of the microintervention on proximal outcomes is moderated by momentary information, such as sleep duration, heart rate variability, and current symptoms of depression and mania. Additionally, we will perform a qualitative analysis of responses to examine comprehension of ACT processes, using an identical coding process described in the Exploratory Analyses section for Study 1. By qualitatively coding responses from both samples, we would also assess how each sample may differ in how participants comprehend and engage in ACT processes.

Results

The study app was released to Google Play and iTunes in fall 2019 and is password protected to restrict use to study participants. Recruitment for the bipolar sample began on September 10, 2019. As of November 16, 2019, we had 10 people enrolled and consented, and participation in the study began on September 13, 2019. Recruitment for the college sample began on October 5, 2019. As of November 16, 2019, 223 participants have completed the screening survey, with 39 being eligible. As of November 16, 2019, we had 14 people enrolled and consented in the study, and participation in the study began on October 18, 2019.

Discussion

Overview

These investigations seek to evaluate the feasibility, safety, and effectiveness of optimizing mobile-based microinterventions among two cohorts: a sample of individuals with bipolar disorder and a sample of distressed first-generation college students. The studies address important public health concerns, including large treatment gaps that leave many suffering from psychiatric disease untreated [11], treatments that may be perceived as inaccessible or incompatible with other life demands, and inadequate proximal assessment of symptom changes directly after intervention. The microintervention design allows for the examination of proximal change in symptoms in the assessment just hours after the intervention was delivered, which presents a distinct advantage when compared to traditional RCTs. Further, the delivery of a microintervention via smartphone meets participants in a familiar environment optimized for on-the-go use. Participants can self-tailor usage to seek additional support when needed, reviewing symptoms or visualizing previously input content. The examinations in this study offer a potentially accessible tool that could reasonably be implemented in future studies among rural samples lacking access to care, among samples with chronic disease or other barriers preventing attendance at weekly psychotherapy, or as an adjunct to brief in-person interventions. As such, the studies will fill critical gaps in the current literature and provide information to be utilized in future studies.

These studies seek to examine a transdiagnostic approach in two different samples in order to determine whether such an intervention is applicable and feasible among individuals of different demographic characteristics and psychiatric symptom profiles. Such an approach is important to consider, given that widely differing psychotherapy approaches for specific psychiatric disorders create further barriers to psychiatric care, given inadequate training, dissemination, and implementation, so that patients can access treatment. Should ACT demonstrate feasibility and preliminary effectiveness, a large RCT applying ACT across diagnoses and demographics would be indicated.

Limitations

Any findings from these studies should be considered in light of several limitations. First, though we designed mobile ACT to support psychological or pharmacological treatment, we will not collect data regarding psychological or pharmacological treatment. Thus, we will not be able to determine if current and prior treatment modifies the effect of mobile ACT. Second, usage data are not being collected beyond logging of symptoms, so time devoted to reviewing or visualizing symptoms will not be examined. The content and word count of responses to the microintervention questions will be tracked, however. Word count alone may not be indicative of engagement quality, which we will explore further with a qualitative analysis. Data collected regarding completion of the introductory ACT video are limited to the average time all participants spent watching the video, the percentage of viewers who watched until the end, and the total number of views. Individual-level data will not be collected, and we will be unable to verify whether participants watched the video and/or completed it in its entirety before using the study app. Furthermore, some of the content may be most effective when viewed in combination with, or subsequent to, other content, and given the randomized nature of the interventions, sequenced interventions are not offered. Nevertheless, we will evaluate the proximal impact of the microinterventions individually, bearing on the question as to whether small-scale interventions are impactful in isolation, both in terms of mood and activity.

Among the bipolar cohort alone, we will have insufficient data to draw conclusions about effectiveness and, as such, the only conclusions drawn will be regarding safety and feasibility. The results will be considered as future studies are designed. In addition, the bipolar cohort received Fitbit activity trackers as part of the study, and the act of wearing a Fitbit may prompt behavioral change in physical activity or sleep. Among the college student cohort, first-generation college student status is self-reported and not verified in order to protect participant privacy. Furthermore, depressive symptoms are measured with a self-report scale and, as such, no diagnostic conclusions can be drawn. The activity measure was developed for this study specifically and is not yet validated, though authors intend to examine the psychometric properties of the scale. Additionally, awareness of avoidance and values-based behaviors may change throughout the intervention, and one of the goals of the interventions is to increase mindful awareness. Similarly, the in-app assessments of manic and depressive symptoms via shortened versions of the YMRS and the SIGH-D have yet to be validated. Additionally, participants in the college student

cohort receive remuneration on a weekly basis, granted they complete at least 50% of study activities (ie, respond to at least seven of the 14 daily prompts from the study app). This incentive to participate may result in increased adherence rates, limiting us from generalizing our findings regarding the feasibility of the intervention to a real-world setting.

Acknowledgments

The research with the bipolar cohort was supported by the Heinz C Prechter Bipolar Research Program at the University of Michigan; the Richard Tam Foundation; and the US Department of Health and Human Services, National Institutes of Health (NIH) (K01 MH112876). The study with the college student cohort was supported by the University of Wisconsin–Madison's Ira and Ineva Reilly Baldwin Idea Endowment Seed Grant (principal investigator: EK). The authors would especially like to thank Tijana Sagorac Gruichich for her help in coordinating the study and for her continued involvement in this research.

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Authors' Contributions

EK, AC, SH, and ZS designed the college student cohort study. EK, AC, SH, and MM designed the bipolar cohort study. EK wrote the microintervention, and AC created the mobile app. SH, EK, AC, and ZS implemented the college student cohort study. AV, AC, and MM implemented the bipolar cohort study. SM, EK, and AC designed the approach to statistical analysis. SH and AV wrote the Methods section. EK wrote the remaining sections. All authors reviewed and approved the manuscript prior to submission.

Conflicts of Interest

ZS has received research support from the NIH, the Centers for Disease Control and Prevention, GlaxoSmithKline (GSK), Pfizer, Wyeth, Janssen Pharmaceuticals, and Sage Therapeutics; has served on speaker or advisory boards for Pfizer, Eli Lilly, Wyeth, Sage Therapeutics, Bristol-Myers Squibb, and GSK; and has received honoraria from Eli Lilly, GSK, Pfizer, and Wyeth. MM has consulted with and/or received grant funding from Janssen Pharmaceuticals and Takeda Pharmaceuticals; he is a co-owner in Priori-AI, LLC.

Multimedia Appendix 1
Summary statement from the National Institutes of Health (NIH) K01 grant (principal investigator: AC). The presented protocol for the bipolar sample is based on Aim 3 of this NIH K01 grant.
[PDF File (Adobe PDF File), 159 KB - resprot_v9i9e17086_app1.pdf]

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Abbreviations

ACT: acceptance and commitment therapy
DIGS: Diagnostic Interview for Genetic Studies
GSK: GlaxoSmithKline
HIPAA: Health Insurance Portability and Accountability Act
NIH: National Institutes of Health
PHQ-2: Patient Health Questionnaire 2
PHQ-9: Patient Health Questionnaire 9
PSS-4: Perceived Stress Scale 4
PSS-10: Perceived Stress Scale 10
RCT: randomized controlled trial

REDCap: Research Electronic Data Capture
SF-36: 36-Item Short Form Survey
SIGH-D: Structured Interview Guide for the Hamilton Depression Rating Scale
YMRS: Young Mania Rating Scale

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Protocol

Game-Based Meditation Therapy to Improve Posttraumatic Stress and Neurobiological Stress Systems in Traumatized Adolescents: Protocol for a Randomized Controlled Trial

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Abstract

Background: Many adolescents in residential care have been exposed to prolonged traumatic experiences such as violence, neglect, or abuse. Consequently, they suffer from posttraumatic stress. This not only negatively affects psychological and behavioral outcomes (eg, increased anxiety, depression, and aggression) but also has adverse effects on physiological outcomes, in particular on their neurobiological stress systems. Although current evidence-based treatment options are effective, they have their limitations. An alternative to traditional trauma treatment is meditation-based treatment that focuses on stress regulation and relaxation. Muse is a game-based meditation intervention that makes use of adolescents' intrinsic motivation. The neurofeedback element reinforces relaxation abilities.

Objective: This paper describes the protocol for a randomized controlled trial in which the goal is to examine the effectiveness of Muse (InteraXon Inc) in reducing posttraumatic stress and normalizing neurobiological stress systems in a sample of traumatized adolescents in residential care.

Methods: This will be a multicenter, multi-informant, and multimethod randomized controlled trial. Participants will be adolescents (N=80), aged 10 to 18 years, with clinical levels of posttraumatic symptoms, who are randomized to receive either the Muse therapy sessions and treatment as usual (intervention) or treatment as usual alone (control). Data will be collected at 3 measurement instances: pretest (T1), posttest (T2), and at 2-month follow-up. Primary outcomes will be posttraumatic symptoms (self-report and mentor report) and stress (self-report) at posttest. Secondary outcomes will be neurobiological stress parameters under both resting and acute stress conditions, and anxiety, depression, and aggression at posttest. Secondary outcomes also include all measures at 2-month follow-up: posttraumatic symptoms, stress, anxiety, depression aggression, and neurobiological resting parameters.

Results: The medical-ethical committee Arnhem-Nijmegen (NL58674.091.16) approved the trial on November 15, 2017. The study was registered on December 2, 2017. Participant enrollment started in January 2018, and the results of the study are expected to be published in spring or summer 2021.

Conclusions: Study results will demonstrate whether game-based meditation therapy improves posttraumatic stress and neurobiological stress systems, and whether it is more effective than treatment as usual alone for traumatized adolescents.

Trial Registration: Netherlands Trial Register NL6689 (NTR6859); https://www.trialregister.nl/trial/6689

International Registered Report Identifier (IRRID): DERR1-10.2196/19881

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KEYWORDS

Adolescents; Autonomic nervous system; Cortisol; Meditation; Neurofeedback; Posttraumatic stress; Randomized controlled trial; Trauma

Introduction

Background

Rates of chronic traumatic exposure among adolescents in residential care are staggering. Over 90% of these adolescents have been exposed to domestic violence, neglect, or emotional, physical, or sexual abuse at a young age [1]. Most of these traumatic experiences take place in the primary caregiving environment, even though caregiver support is essential for adolescents' attachment, resilience, and stress adaptation [2]. Abuse by caregivers is probably the most interfering stressor that they can experience. Early traumatization interferes with adolescents' healthy development [3]. It can have devastating effects on their psychosocial development [2], physical health [4], and neurobiological stress response systems [3,5-7].

Neurobiological Stress Systems

Stress activates the autonomic nervous system and the hypothalamic-pituitary-adrenal axis to produce an appropriate stress response. The autonomic nervous system consists of the sympathetic nervous system and the parasympathetic nervous system. Activation of the sympathetic nervous system occurs rapidly after stress exposure—usually within milliseconds to seconds. When confronted with a stressor, the sympathetic nervous system activates physiological processes frequently referred to as the *fight or flight* response [8]. The increase in sympathetic nervous system activity is reflected by a shorter pre-ejection period (the length of time between the contraction of the heart and the ejection of blood out of the heart into the aorta), corresponding with a higher heart rate [9]. When the stressor disappears, the parasympathetic nervous system inhibits sympathetic activation and facilitates bodily homeostasis (ie, recovery and digestion) [8]. Generally, it has been assumed that the sympathetic nervous system and parasympathetic nervous system are reciprocally coupled: when sympathetic nervous system activity increases, parasympathetic nervous system activity decreases, and vice versa. However, various individual variations of autonomic nervous system and parasympathetic nervous system contributions to stress responses exist [10,11]. One key parameter of the parasympathetic nervous system is respiratory sinus arrhythmia, also referred to as vagal tone. Respiratory sinus arrhythmia is a measure of heart rate variability that represents parasympathetic nervous system control over heart rate and occurs at the frequency of respiration and that facilitates adaptive responses to the environment [12,13]. Lower respiratory sinus arrhythmia is associated with more internalizing and externalizing problems [14] and may increase the risk on internalizing problems after trauma [15,16].

The response of the hypothalamic-pituitary-adrenal axis is slower and has a longer duration than that of the sympathetic nervous system [8,17]. The primary effectors of the hypothalamic-pituitary-adrenal axis system are glucocorticoids (steroid hormones). These have a slower onset and longer duration than the catecholamines of the sympathetic nervous system. Stress activates the paraventricular nucleus of the hypothalamus, which releases corticotropin-releasing hormone within a few minutes, usually peaking 15 minutes after the stressor [18]. This stimulates the production of adrenocorticotropic hormone by the pituitary, which in turn signals the adrenal gland to release cortisol. Cortisol is also produced during nonstressful situations, referred to as basal cortisol [17]. Research in adolescents on the impact of trauma on cortisol shows evidence for a link between trauma and hypothalamic-pituitary-adrenal axis alterations but is characterized by the lack of a clear physiological profile. Exposure to trauma has been related to increased [19,20] and decreased cortisol levels [19-21].

In healthy individuals, the autonomic nervous system and the hypothalamic-pituitary-adrenal axis together generate adaptive responses in the face of acute threat. However, the experience of multiple, prolonged traumatic events can result in chronic activation of these stress systems, even when the original stressor has disappeared [2]. The unpredictable and ongoing nature of the traumatic events make these adolescents feel as if they are under constant threat of survival [22]. Unsurprisingly, the adverse effects of trauma become more severe and pervasive as the trauma lasts for a long period or the number of traumatic events increases [1,23].

Trauma Treatment

Although trauma-focused cognitive behavioral therapy and eye movement desensitization and reprocessing are well-established effective treatments for traumatized adolescents [24], there are some inherent limitations. Both treatment models incorporate exposure techniques, verbal expression, and rely on the integration of cognition, emotion, and physiology. In order for the therapy to succeed in promoting change, sufficient capacity to regulate these systems is required [25]. Yet, traumatized adolescents often lack the capacity to control and regulate their impulses and emotions [2,26], and even when adolescents do exhibit the necessary skills in order for therapy to succeed in promoting change, residential care provides an often chaotic living environment that impedes the development of a therapeutic relationship and treatment progress [27]. Also, adolescents are often not motivated to talk about their experiences and re-experience their traumatic past [28].

Given the difficulties faced in traditional trauma treatment, alternative forms of intervention have gained popularity. The focus has shifted from mainly cognitive-oriented and verbally dependent therapies to interventions that target physiological

sensations. One promising approach is fostered by meditation interventions that focus on adolescents' stress regulation abilities. Meditation techniques (eg, deep-breathing practices) focus on one's own bodily sensations and increase a sense of control over the body. Not only can feelings of stress be reduced and emotion-regulation capacities improved, individuals also showed beneficial changes in cardiovascular activity [29-31]. Meditation can restore activity and connectivity in brain regions associated with posttraumatic symptoms [32], lead to more balanced patterns of neurobiological stress responses [33], and modulate both hypothalamic-pituitary-adrenal axis and autonomic nervous system reactivity [34]. Research on the effectiveness of meditation interventions for posttraumatic stress shows encouraging findings. Most studies have been conducted among adults [32-36], but promising outcomes have been reported in traumatized adolescents too [37].

Game-Based Therapy

This study aims to test the efficacy of game-based neurofeedback meditation therapy as an addition to treatment as usual in a population of traumatized adolescents in residential care. Gaming forms a novel strategy to engage adolescents into treatment and holds several advantages over traditional therapy. Videogame or gamified interventions make use of adolescents' intrinsic motivation [38], while conventional treatment often depends upon imparting psychoeducational information, a didactic style of learning that contains few elements that are intrinsically motivating. Yet, motivation is an important predictor of treatment effectiveness [39], and adolescents in residential institutions are usually characterized by a lack of motivation to change their behavior [40]. Gamified treatment teaches adolescents techniques and skills but with less thinking and more doing [38]. This way of learning suits them better than memorizing certain principles [41]—conventional therapy—does [42]. Game-play is characterized by its repetitive nature. Repetition promotes long-term learning [43], and thus may foster generalization of its effects to adolescents' daily lives. There have been some studies [44-46] conducted among adolescents in residential institutions that evaluated biofeedback videogame interventions. Results showed high user satisfaction, minimal attrition, and improved emotion-regulation [44-46].

Recently, the authors conducted a feasibility study [47] that evaluated 3 game-based meditation interventions in traumatized adolescents in residential care. The interventions incorporated either bio- or neurofeedback and were assessed on their potential to improve physiological stress regulation, user satisfaction, and preliminary effectiveness on posttraumatic symptoms, stress, depression, and aggression. The intervention that was evaluated positive on all outcomes and considered the best fit was Muse (InteraXon Inc)—a game-based neurofeedback meditation intervention.

Objectives

The primary aim of this study is to investigate the effectiveness of Muse as an addition to treatment as usual in reducing posttraumatic symptoms (self- and mentor report) and stress (self-report) compared with treatment as usual in traumatized adolescents in residential care. We expect that playing Muse will result in a greater reduction of posttraumatic symptoms and stress than treatment as usual alone.

As a secondary aim, we will investigate the effectiveness of Muse on neurobiological stress systems under both resting and social stress conditions. It is hypothesized that participants who play Muse will show normalized neurobiological parameter compared to participants in the control group. We will also assess the effects of playing Muse on anxiety (self-report), depression (self-report) and aggression (self- and mentor report). It was expected that playing Muse would result in reduced anxiety, depression, and aggression.

Methods

Study Design

This study is a multicenter randomized controlled trial with 2 parallel intervention groups. Outcomes will be compared at 3 measurement instances: before the intervention (T1), immediately after the intervention (T2), and at a 2-month follow-up. Participants will be randomly assigned to the intervention or the treatment-as-usual (control) group, stratified by gender and intellect to ensure equal ratios of participants in both groups.

Study Setting

Recruitment will take place in 3 residential institutions in The Netherlands that provide open and secured care for children and adolescents with and without intellectual disability. Residential care is the most intensive form of youth care and includes out-of-home placement and 24-hour care. These adolescents are unable to live at home due to severe psychiatric or behavioral problems, parental problems, or an unsafe home environment—often a combination of all of these. Adolescents live in group homes with group care workers as substitute care givers and receive treatment to target problem behavior. Residential care is often seen as a last-resort solution when there are no other options for treatment [48].

Inclusion and Exclusion Criteria

Inclusion criteria are (1) clinical levels of posttraumatic symptoms, measured as a score of 30 or higher on the Children's Revised Impact of Event Scale (CRIES-13) [49]; (2) age between 10 and 18 years; (3) capable of understanding and speaking Dutch; (4) active informed assent to participate in the study from participants themselves and active consent from legal guardians when participants are under the age of 16 (obtained by the first author). Exclusion criteria are (1) negative clinician advice, for example, when the participant already has other forms of treatment and the clinical fears that treatment burden would become too heavy (at this stage, participants are not randomized yet, so this exclusion criterion will affect both groups equally); (2) simultaneous participation in another clinical intervention study; (3) acute psychotic symptoms; (4) current or recent (within the previous 3 months) trauma treatment, specifically eye movement desensitization and reprocessing or trauma-focused cognitive behavioral therapy specifically targeting posttraumatic symptoms. There are no restrictions for other types of interventions that participants may receive (eg, medication, individual therapy, or group therapy).

We will keep track of additional interventions and use them as covariates in the analyses, if necessary.

Recruitment

At adolescents' admission to the residential institutions taking part in the study, the CRIES-13 is included in the standard questionnaire battery that adolescents fill out at intake. Adolescents with a clinical score of posttraumatic symptoms on the CRIES-13 (≥30), filled in less than 3 months before T1, will be considered eligible participants for this study. We will include adolescents with clinical levels of posttraumatic symptoms rather than adolescents who qualify for the diagnosis of posttraumatic stress disorder because many adolescents who do not meet the criteria for posttraumatic stress disorder do suffer from posttraumatic symptoms and are in need of treatment [50].

Additionally, clinicians will be asked whether the adolescent in question can be invited to take part in this study. After clinician consult, eligible participants will be contacted by the coordinating researcher who will explain the studies. We will obtain verbal and written assent from all participants, and when they are younger than the age of 16, also written consent from their legal guardians. Potential participants will be invited for an individual meeting with the coordinating researcher who will explain the study. Participants will be explicitly informed about the study design and that they can quit study participation at any moment without disadvantages. The researcher will also bring information letters with information on all aspects of the study. When adolescents initially agree to participate, they will be given the information letters, and 2 to 3 weeks later, they will be asked for their written assent and invited for the pretest measurement (T1).

Allocation and Randomization

If all inclusion and no exclusion criteria are fulfilled, participants will be randomly assigned (1:1 ratio) to 1 of the 2 groups using a randomization schedule that is generated by a Python script and stratified by gender, intellect, and residential institution. Allocation to groups is not masked, but participants and their mentors will not be informed about the specific expectations regarding posttraumatic symptoms and neurobiological stress reactivity. We will explain that Muse is a relaxation app, designed to help participants deal with stress. Participant enrollment and assignment to the groups will be performed by the first author.

Interventions

All participants receive treatment as usual: the treatment as recommended by their clinicians regardless of this study (eg, individual or family therapy; medication). There are no restrictions for the type of interventions that participants can receive other than trauma-focused treatment, we only keep track of them. Participants in the intervention group will receive the intervention sessions as an addition to treatment as usual.

Muse is a game-based meditation app that is played on an iPad with a electroencephalography (EEG)–based headband that utilizes real-time neurofeedback. The intervention takes 6 weeks and consists of two 15- to 20-minute gameplay sessions per week. If participants are unable to make it to a session, this session will be rescheduled. All participants will complete 12 gameplay sessions in total. These sessions will take place in an office room located on the campus of the residential institution. Muse includes 10 relaxation tutorials that resemble elements of trauma-focused cognitive behavioral therapy such as deep-breathing techniques [42]. The tutorials are followed by 3-minute meditation sessions. The meditation tutorials are in English, so we have created a standardized protocol with Dutch translations of each tutorial. The gameplay sessions will be supervised by research assistants who are trained to explain the tutorials according to this protocol.

Participants can choose the in-game environment that will be shown during the meditation sessions (eg, beach, rainforest, city park). Before each tutorial, a short calibration will take place, during which the headband records the participants' brain activity during rest, as a reference point for the upcoming meditation session. The tutorials are followed by 3-minute meditation sessions. Participants will complete at least 2 tutorials and subsequent meditation sessions each intervention session. During the meditation sessions, participants hear sounds in the in-game environment that they have chosen. The EEG-based headband provides real-time neurofeedback that is reflected by the intensity of activity in the environment. When the participant's mind is calm, the environment shows calm and settled winds, but these winds will pick up and blow when the participant's mind becomes more active. When participants succeed in remaining in a calm state for a sufficient amount of time, they will hear birds whistling. The neurofeedback element of the intervention involves retraining brain patterns through operant conditioning. Neurofeedback reinforces individuals' relaxation abilities [51] and can reduce posttraumatic symptoms [52].

After each meditation session, participants get feedback on their performance through a series of simple graphs. In order to motivate, Muse calculates points, provides awards, and sets goals and challenges. Performances are saved and tracked so participants can see their progress over time.

Study Procedure

See Table 1 for an overview of all measurements and outcomes. The pretest (T1) will take place in week 1 and will include an interview, an aquatic video, a social stress task, and a hair cortisol measurement. During the interview, the self-report questionnaires will be administered. We will conduct interviews rather than let participants fill in the questionnaires themselves, to ensure cooperation and comprehension. The interview format is, in particular, suitable for adolescents with lower intelligence, since this makes it easier for them to ask for additional explanation when they do not understand the question. Adolescents in residential care are often school dropouts and some of them may have trouble with reading, while they can easily answer the questions when these are read out aloud. The interviews will take approximately 30 minutes, with breaks in-between, and will be conducted by the coordinating researcher.

Table 1. Overview of all measurement moments and outcomes.

Time point	Study timeline	Procedure	Measures
T0	≤3 months before T1	Screening	Questionnaire
			Posttraumatic stress (CRIES-13[a])
T1	Week 1	Pretest measurement	Questionnaires
			Posttraumatic symptoms (CROPS[b] and PROPS[c])
			Stress, depression, anxiety (DASS-21[d])
			Aggression (RPQ[e] and PRPA[f])
			Neurobiological activity during rest
			Basal ANS[g] activity
			Basal HPA[h] axis activity
			Neurobiological reactivity to acute stress
			ANS reactivity
			HPA axis reactivity
—	Week 2-7	Intervention	—
T2	Week 8	Posttest measurement	Questionnaires
			Posttraumatic symptoms (CROPS and PROPS)
			Stress, depression, anxiety (DASS-21)
			Aggression (RPQ and PRPA)
			Neurobiological activity during rest
			Basal ANS activity
			Basal HPA axis activity
			Neurobiological reactivity to acute stress
			ANS reactivity
			HPA axis reactivity
Follow-up	Week 16	Two-month follow-up	Questionnaires
			Posttraumatic symptoms (CROPS and PROPS)
			Stress, depression, anxiety (DASS-21)
			Aggression (RPQ and PRPA)
			Neurobiological activity during rest
			Basal ANS activity
			Basal HPA axis activity

[a]CRIES-13: Children's Revised Impact of Event Scale.

[b]CROPS: Child Report of Posttraumatic Symptoms.

[c]DASS-21: Depression Anxiety Stress Scales.

[d]PROPS: Parent Report of Posttraumatic Symptoms.

[e]PRPA: Parent-rating scale for Reactive and Proactive Aggression.

[f]RPQ: Reactive and Proactive Aggression Questionnaire.

[g]ANS: autonomic nervous system.

[h]HPA: hypothalamic-pituitary-adrenal.

Participants will watch an aquatic video for 5 minutes [53] to derive basal autonomic nervous system parameters during rest, in order to compare to the autonomic nervous system parameters derived during the stress task. The social stress task is an adapted and combined version of the Trier Social Stress Task for Children (TRIER-C) [54,55] and the Sing-a-Song Stress Test (SSST) [56]. Participants receive the introduction of a story and are told that they have 5 minutes to compose the end of the story. Then, they will present their story for 4 minutes in front of a camera. Unlike the original TRIER-C, the judge panel will

be replaced by a video camera [57]. Participants will be recorded, allegedly for later assessment by a group of peers who will judge their performance. If the participant does not complete the 4 minutes for presenting, the researcher can use a standard set of prompts to encourage further narration. Immediately after the 4 minutes, participants will be asked to fill in a 3-item manipulation check to rate how nervous the presentation task has made them on a scale from 1 (not nervous at all) to 10 (very nervous). Next, participants are given a booklet with song texts and are told that they have to sing a song in front of the camera. Participants have 30 seconds to choose a song and are expected to sing the song aloud for 30 seconds. Again, they will be asked to fill out the manipulation check immediately after the task. For an overview of the stress task, see Table 2. Participants will not be fully debriefed until they completed the second stress task at T2.

Table 2. Overview of the social stress task to measure neurobiological reactivity to acute stress.

Task timeline	Activity	ANS[a] recordings	Cortisol samples
Before			
–20 minutes	—	—	–20
–5 minutes	Aquatic video	Basal ANS parameters	—
0 minutes	—	—	Pre
Start			
	Anticipation speech task	ANS reactivity	—
	Speech task	ANS reactivity	—
	Manipulation check	—	—
	Anticipation song task	ANS reactivity	—
	Song task	ANS reactivity	—
	Manipulation check	—	—
After			
0 minutes	Recovery	ANS recovery	Post
10 minutes	—	—	+10
20 minutes	—	—	+20
40 minutes	—	—	+40

[a]ANS: autonomic nervous system.

The posttest (T2) will take place in week 8 and includes, like the pretest (T1), an interview, aquatic video, social stress task, and a hair cortisol measurement. Since participants will be exposed to the social stress task twice, it is expected that they show habituation-related decreased levels of stress at T2 [58,59]. To lower the risk for stress habituation and to improve methodological rigor for the second social stress task, participants will be given another story introduction that is comparable to the story that will be used for T1. At the end of T2, participants will be debriefed and told that the video recordings were deleted immediately after the measurement session.

The 2-month follow-up will take place in week 16 and includes an interview, aquatic video, and a hair cortisol measurement. The 2-month follow-up measurement is conducted to provide additional information about potential long-term intervention effects. Therefore, we will use questionnaires and the parameters to measure neurobiological activity during rest that are relatively simple to obtain (ie, a 5-minute autonomic nervous system measurement during the aquatic video and cutting the hair). Measuring neurobiological reactivity requires the execution of a stress task that is time-consuming, and even more important, eliciting stress among traumatized adolescents is not without risks and should only be done when essential for research purposes. For those reasons, neurobiological reactivity to acute stress was not included at 2-month follow-up measurement.

Participants will receive a gift voucher of €15 (approximately US $17.86) at T1, a gift voucher of €10 (approximately US $11.91) and a stress ball at T2, and a gift voucher of €15 at 2-month follow-up measurement. Participants' mentors (ie, the group home worker with whom they have the most contact) will fill in the questionnaires in the same week as when the measurements with the participants are conducted.

Measures

Questionnaires

The screening instrument is the CRIES-13 [49], a questionnaire with 13 four-point items to screen whether adolescents suffer from posttraumatic symptoms.

Posttraumatic symptoms will be measured by participants' self-report as well as by mentor report. The Child Report of Posttraumatic Symptoms (CROPS) [60] is a self-report questionnaire that consists of 24 three-point items. The Parent Report of Posttraumatic Symptoms (PROPS) [60] is a 30-item questionnaire that measures posttraumatic symptoms as reported

by parents or other caretakers. In this study, participants' group home mentors will fill out the questionnaire. Several studies have demonstrated the validity and reliability of the CROPS and the PROPS in general populations [61]. Additionally, the CROPS has been validated in a sample of juvenile offenders [62]. The CROPS and the PROPS have been jointly developed so that the CROPS focuses on internal thoughts and feelings, whereas the PROPS focuses on observable behaviors.

Stress will be examined with the 7-item stress subscale of the Depression Anxiety Stress Scales (DASS-21) [63,64]. The DASS-21 is a self-report questionnaire that in total consists of 21 four-point items. Its validity and reliability are good and the subscales have an excellent internal consistency [63].

Anxiety will be measured with the 7-item anxiety subscale of the DASS-21 [63,64].

Depression will be measured with the 7-item depression subscale of the DASS-21 [63,64].

Aggression will be measured by participants self-report as well as by mentor report. The Reactive and Proactive Aggression Questionnaire (RPQ) [65] is a self-report questionnaire that is composed of 23 three-point items. The RPQ consists of proactive aggression and reactive aggression subscales. Its validity and reliability are good, and both subscales have good internal consistency [65]. The Parent-rating scale for Reactive and Proactive Aggression (PRPA) [66] is a questionnaire that can be filled out by parents or other caretakers. The PRPA has 11 three-point items and consists of reactive aggression and proactive aggression subscales. The PRPA total score and both its subscale scores have good validity [66].

Neurobiological Activity During Rest

Autonomic nervous system parameters will be measured with the *Vrije Universiteit* Ambulatory Monitoring System (VU-AMS) [67,68]. This a lightweight ambulatory device that records electrocardiograms and changes in thorax impedance with 5 electrodes that are placed on participants' chest and 2 that are placed on the back. The electrocardiogram has a sampling rate of 1000 Hz and heart rate is obtained from the time between 2 adjacent R peaks. Heart rate data will be extracted and visually inspected for artifacts with the *Vrije Universiteit* Data Analysis and Management Software program (VU-DAMS; version 4.0) [69]. We will derive heart rate, respiratory sinus arrhythmia, pre-ejection period, respiration rate, and skin conductance parameters from the VU-AMS recordings.

Basal autonomic nervous system parameters during rest will be derived from VU-AMS recordings while participants are watching an aquatic video for 5 minutes [53].

For basal hypothalamic-pituitary-adrenal axis activity, basal cortisol levels will be measured in participants' hair. Whereas saliva captures real-time cortisol levels that are subject to major fluctuations [70], hair cortisol provide a reliable way to assess average long-term activity of the hypothalamic-pituitary-adrenal axis (thus cortisol exposure over longer time). Hair samples will be cut as close to the scalp as possible from a posterior vertex position. At least 15 mg of the most proximal 1.5 cm of each hair sample will be used for analysis—representing the basal level over the 6 weeks before the hair sample was taken. Hair processing and analyses will be conducted by the Laboratory of Endocrinology of the Erasmus Medical Center, Rotterdam, the Netherlands. Hair samples will be washed in isopropanol and after solid phase extraction, hair cortisol will be quantified by liquid chromatography–tandem mass spectrometry [71].

Neurobiological Reactivity to Acute Stress

For autonomic nervous system reactivity to acute stress, autonomic nervous system parameters will be measured while participants complete the social stress task (see Table 2). We will derive autonomic nervous system parameters during the following segments of the stress task: (1) anticipation speech task, (2) performing speech task, (3) anticipation song task, (4) song task, and (5) recovery.

For hypothalamic-pituitary-adrenal axis reactivity to acute stress, salivary cortisol levels will be measures before and after completion of the social stress task (see Table 2). Six saliva samples will be obtained with a collection device (Salivette; Sarstedt AG and Co) twenty minutes (–20), immediately before the social stress task (pre), immediately after (post), ten minutes (+10), twenty minutes (+20), and forty (+40) minutes after the task (Table 2). Cortisol levels will be measured using the liquid chromatography–tandem mass spectrometry method with CHS MSMS Steroid kit (PerkinElmer).

Sample Size Calculation

Power calculations were performed using G*Power [72]. An a priori power analysis for analysis of variance (repeated measures, within-between interaction) was conducted. Based on previous meditation-based interventions for posttraumatic stress [32,34-36,73], we expected a small to medium effect size of d=0.30 and a repeated measures correlation of 0.60. To achieve a statistical power of at least .80, a sample size of 72 participants was required. We aim to include 80 participants in total to allow for 10% attrition, which was estimated from previous studies [44,45,47] on game-based interventions in this population.

Statistical Analysis

To assess intervention efficacy, we will use repeated measure analysis of variance to detect differences in mean outcome scores between the 2 groups at T2 and at 2-month follow-up. All analyses will be conducted in accordance with the intention-to-treat principle. Missing data will be imputed using Markov Chain Monte Carlo [74]. Results will be expressed as differences in mean scores between the 2 groups with 95% confidence intervals. P values<.05 will be considered statistically significant.

Ethical and Safety Issues

Ethical review and approval of this study has been provided by the medical-ethical committee Arnhem-Nijmegen (protocol NL58674.091.16). All substantial amendments will be presented to the committee and competent authority. Before participants are included in the study, they will be informed about the study design, including randomization. Participants who are assigned

to the control group will be offered the opportunity to play Muse after the study has ended. Participants can withdraw from participation at any time without consequences.

Participant privacy will be protected by allocating identification numbers to personal information that is traceable in a separate file using double-key encryption. Data will be analyzed in a way that no conclusions can be drawn about individual participants. The 3 researchers that will have access to the data work at the residential institutions where the study is being conducted. Data entry will be double-checked to ensure accuracy. Biological materials will be stored in a locked cabinet or a locked medical freezer at Pluryn until the end of the study. The material will be destroyed after laboratory analysis, as requested by the medical-ethical committee that approved the study.

Adverse events reported by participants or group care workers or observed by the researchers will be recorded and assessed in collaboration with participant's clinician. The potential relation to the intervention will be examined and participants will be followed until they are reached stable. The risk in participating for this study is considered negligible, but if a participant seems negatively affected by the measurements or intervention, study participation will be discussed with the clinician and discontinued, if necessary.

Results

This study has been registered (Netherlands Trial Register NL6689 [NTR6859]). This study was approved by the medical-ethical committee Arnhem-Nijmegen (NL58674.091.16) on November 15, 2017. Participant enrollment started in January 2018. The results of the study will be published in international journals and presented at international conferences. Research findings are expected to be published in the spring or summer of 2021.

Discussion

This study is the first to examine the effectiveness of a game-based meditation intervention in a clinical population of traumatized adolescents in residential care. To test the effectiveness of interventions within this population is crucial, since early alterations of these systems increase the risk of psychopathology at a later age [75]. At an early age, neurobiological stress systems contain high rates of plasticity [76], so adolescents could benefit substantially from effective treatment.

A particular strength of this study is that we use a multimodal, multi-informant approach with different types of assessment (ie, questionnaires and physiological measures) and different informants (ie, self-report and mentor-report). This type of approach is the most accurate way to assess and monitor adolescent mental health [77]. Additionally, we will measure hypothalamic-pituitary-adrenal axis and autonomic nervous system reactivity, since both neurobiological stress systems are hypothesized to play a role in the development and maintenance of posttraumatic symptoms [3]. To gain understanding in how trauma affects neurobiology, multisystem approaches need to be considered [78].

Limitations to the design of this study are the nonactive control group, and because of that, the lack of group concealment. Active control groups are more rigorous and leave no room for alternative explanations regarding attention, motivation, and behavioral expectation, but only when participants in both groups have the same expectations of improvement [79]. An optimal control group would require a game-based intervention that is comparable to that of Muse, but without its hypothesized working mechanisms. This is not feasible since this study will be conducted in residential institutions that have tight restrictions for casual gameplay. Clinicians do not agree on implementing a gameplay intervention that is not expected to be beneficial for participants. The primary purpose of this study, however, is to test the effectiveness of Muse as an addition to treatment as usual, not to determine its superiority to another form of treatment. Therefore, treatment as usual can be considered as a valid control group [80]. Due to the inactive control group, masking of groups is not possible. Participants and mentors will be aware of the groups to which the participants are assigned. Thus, it might be possible that differential expectations will bias study outcomes.

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Conflicts of Interest

None declared.

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Abbreviations

CRIES-13: Children's Revised Impact of Event Scale
CROPS: Child Report of Posttraumatic Symptoms
DASS-21: Depression Anxiety Stress Scales
PROPS: Parent Report of Posttraumatic Symptoms
PRPA: Parent-rating scale for Reactive and Proactive Aggression
RPQ: Reactive and Proactive Aggression Questionnaire
SSST: Sing-a-Song Stress Test
TRIER-C: Trier Social Stress Task for Children
VU-AMS: Vrije Universiteit Ambulatory Monitoring System
VU-DAMS: Vrije Universiteit Data Analysis and Management Software

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Protocol

Stories to Communicate Individual Risk for Opioid Prescriptions for Back and Kidney Stone Pain: Protocol for the Life STORRIED Multicenter Randomized Clinical Trial

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Abstract

Background: Prescription opioid misuse in the United States is a devastating public health crisis; many chronic opioid users were originally prescribed this class of medication for acute pain. Video narrative–enhanced risk communication may improve patient outcomes, such as knowledge of opioid risk and opioid use behaviors after an episode of acute pain.

Objective: Our objective is to assess the effect of probabilistic and narrative-enhanced opioid risk communication on patient-reported outcomes, including knowledge, opioid use, and patient preferences, for patients who present to emergency departments with back pain and kidney stone pain.

Methods: This is a multisite randomized controlled trial. Patients presenting to the acute care facilities of four geographically and ethnically diverse US hospital centers with acute renal colic pain or musculoskeletal back and/or neck pain are eligible for this randomized controlled trial. A control group of patients receiving general risk information is compared to two intervention groups: one receiving the risk information sheet plus an individualized, visual probabilistic Opioid Risk Tool (ORT) and another receiving the risk information sheet plus a video narrative–enhanced probabilistic ORT. We will study the effect of probabilistic and narrative-enhanced opioid risk communication on the following: risk awareness and recall at 14 days postenrollment, reduced use or preferences for opioids after the emergency department episode, and alignment with patient preference and provider prescription. To assess these outcomes, we administer baseline patient surveys during acute care admission and follow-up surveys at predetermined times during the 3 months after discharge.

Results: A total of 1302 patients were enrolled over 24 months. The mean age of the participants was 40 years (SD 14), 692 out of 1302 (53.15%) were female, 556 out of 1302 (42.70%) were White, 498 out of 1302 (38.25%) were Black, 1002 out of 1302 (76.96%) had back pain, and 334 out of 1302 (25.65%) were at medium or high risk. Demographics and ORT scores were equally distributed across arms.

Conclusions: This study seeks to assess the potential clinical role of narrative-enhanced, risk-informed communication for acute pain management in acute care settings. This paper outlines the protocol used to implement the study and highlights crucial methodological, statistical, and stakeholder involvement as well as dissemination considerations.

Trial Registration: ClinicalTrials.gov NCT03134092; https://clinicaltrials.gov/ct2/show/NCT03134092

International Registered Report Identifier (IRRID): DERR1-10.2196/19496

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KEYWORDS

prescription opioids; opioid misuse; acute pain: opioid risk; probabilistic risk tool; renal colic; musculoskeletal back pain; narratives; randomized controlled trial

Introduction

Opioid misuse in the United States is a devastating public health crisis, responsible for over 70,000 overdose deaths per year and US $78.5 billion in health and social costs annually from prescription opioids alone [1,2]. Almost 218,000 people in the United States died from overdoses related to prescription opioids between 1999 and 2017 [3]. Notably, most chronic prescription opioid users were originally prescribed the medication for acute pain [4,5].

With 42% of emergency department visits related to pain, acute care settings are vital locations for providers and patients to manage pain while avoiding the risk of future misuse of opioids [6]. In acute illness and recovery, inadequate pain management is associated with greater morbidity, lower patient satisfaction, and higher costs of care [7]. Nevertheless, younger age, illicit drug use, tobacco use, alcohol misuse, sexual abuse, and family history of drug and alcohol use are all risk factors for prescription drug misuse, along with social factors including unemployment and mental health conditions, such as depression, anxiety, and posttraumatic stress disorder [8,9].

In practice, providers may make therapeutic decisions, particularly around analgesia, without engaging patients about their risks. Providers may engage patients minimally by, for example, distributing information sheets about risks related to procedures or treatment plans. However, a recent emergency department randomized controlled trial demonstrated that a fact-based, literacy-appropriate information sheet alone did not improve patients' knowledge and safe use of opioid analgesics compared to usual care [10]. Moreover, when providers do discuss the risks and benefits of specific options with their patients, the communication is frequently devoid of context and is probabilistic in nature (ie, presenting the likelihood of outcomes using either descriptive words or numbers) [11,12]. Moreover, while probabilistic tools have been established as a common way to communicate information about risks and benefits to patients facing medical decisions, they often lack an individualized component that prompts patients to think about their own risk. We are conducting the Life STORRIED (*Life Stories for Opioid Risk Reduction in the ED* [emergency department]) study to test the effectiveness of a risk tool that incorporates a patient's individualized risk with and without a video narrative.

Narrative communication can be an inexpensive, sustainable, and effective tool to promote engagement around health information and to enhance other forms of risk communication. A health communication narrative is defined as a coherent story with an identifiable beginning, middle, and end that provides information about scene, characters, and conflict; raises unanswered questions or unresolved conflict; and provides resolution [13]. Narratives have been noted to improve the communication of health information by holding people's attention and "transporting" their mental state [14,15]. Importantly, narratives have been shown to help clarify the values and trade-offs associated with risk in a more palatable manner than purely probabilistic facts alone [16] and can be a risk communication tool that helps patients consider their own health behaviors. Communicating risk using narratives has also been demonstrated to benefit subgroups with lower levels of education, literacy, and numeracy [16-21]. However, the role of narratives for communicating and translating risk evidence, specifically when attempting to improve pain treatment in acute care settings, has not been evaluated in a comparative manner. Therefore, we are interested in understanding whether narratives can enhance the use of an individualized, visual probabilistic risk tool (PRT) for communication about acute pain treatment.

This study assesses two clinical interventions for opioid risk management among patients presenting to acute care settings with nonsurgical musculoskeletal back pain or renal colic: an individualized, visual PRT and a video-based narrative-enhanced risk tool (NERT). The PRT is a risk communication intervention derived from the previously validated Opioid Risk Tool (ORT) [22]. Leveraging the science showing that narratives can enhance the effect of probabilistic communication [17-21], the NERT combines the PRT—a probabilistic and individualized risk tool—with a menu of video narratives, generated from past patients' stories and displayed during the clinical encounter on a tablet computer.

This manuscript outlines the protocol used to implement the Life STORRIED study, toward the goal of better understanding the clinical potential of narrative-enhanced, risk-informed communication in the setting of acute pain. The overall goal of this study is to assess the effect of probabilistic and narrative-enhanced opioid risk communication on patient-reported outcomes, including knowledge, opioid use, and patient preferences, for patients who present to emergency departments with back pain and kidney stone pain.

Methods

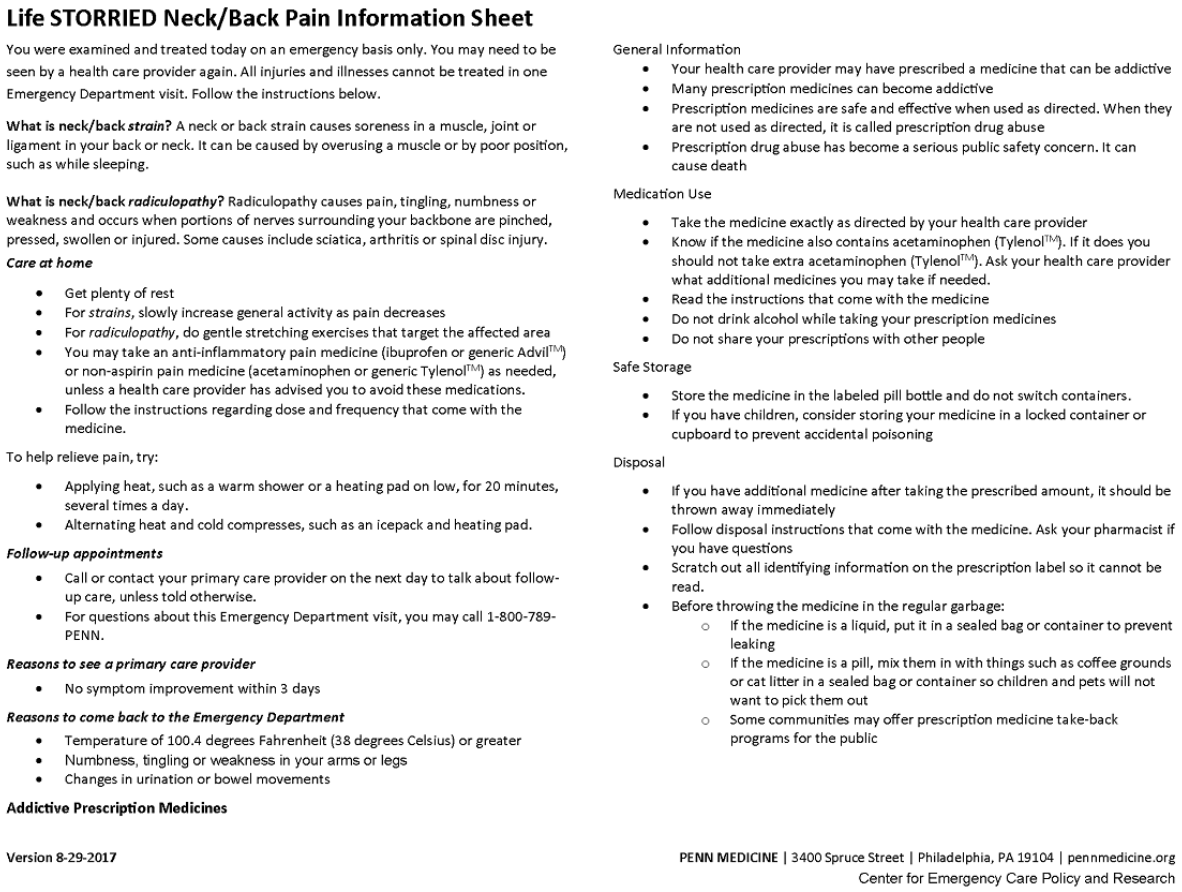
The Life STORRIED study is a multicenter randomized clinical trial in the United States. Central ethical approval has been confirmed by the University of Pennsylvania Institutional Review Board (IRB). The study was registered at ClinicalTrials.gov (NCT03134092).

Experimental Plan

Eligible patients presenting to participating sites (ie, emergency departments and associated observation units) from four geographically distinct health systems have been randomized to one of three study arms:

1. Control group (Arm 1): patients receive a standardized, general risk information sheet (ie, general risk comparator) only. This study arm represents a risk communication approach commonly employed in clinical practice (see Figures 1 and 2).
2. PRT intervention group (Arm 2): patients receive a standardized, general risk information sheet plus an individualized, visual probabilistic ORT (see Figures 3-5).
3. NERT intervention group (Arm 3): patients receive a standardized, general risk information sheet plus a video narrative–enhanced probabilistic ORT (see Figure 6 [23-30]).

Figure 1. General risk comparator back pain information sheet for the Life STORRIED (Life Stories for Opioid Risk Reduction in the ED [emergency department]) study.



Life STORRIED Neck/Back Pain Information Sheet

You were examined and treated today on an emergency basis only. You may need to be seen by a health care provider again. All injuries and illnesses cannot be treated in one Emergency Department visit. Follow the instructions below.

What is neck/back *strain*? A neck or back strain causes soreness in a muscle, joint or ligament in your back or neck. It can be caused by overusing a muscle or by poor position, such as while sleeping.

What is neck/back *radiculopathy*? Radiculopathy causes pain, tingling, numbness or weakness and occurs when portions of nerves surrounding your backbone are pinched, pressed, swollen or injured. Some causes include sciatica, arthritis or spinal disc injury.

Care at home

- Get plenty of rest
- For *strains*, slowly increase general activity as pain decreases
- For *radiculopathy*, do gentle stretching exercises that target the affected area
- You may take an anti-inflammatory pain medicine (ibuprofen or generic Advil™) or non-aspirin pain medicine (acetaminophen or generic Tylenol™) as needed, unless a health care provider has advised you to avoid these medications.
- Follow the instructions regarding dose and frequency that come with the medicine.

To help relieve pain, try:

- Applying heat, such as a warm shower or a heating pad on low, for 20 minutes, several times a day.
- Alternating heat and cold compresses, such as an icepack and heating pad.

Follow-up appointments

- Call or contact your primary care provider on the next day to talk about follow-up care, unless told otherwise.
- For questions about this Emergency Department visit, you may call 1-800-789-PENN.

Reasons to see a primary care provider

- No symptom improvement within 3 days

Reasons to come back to the Emergency Department

- Temperature of 100.4 degrees Fahrenheit (38 degrees Celsius) or greater
- Numbness, tingling or weakness in your arms or legs
- Changes in urination or bowel movements

Addictive Prescription Medicines

Version 8-29-2017

General Information

- Your health care provider may have prescribed a medicine that can be addictive
- Many prescription medicines can become addictive
- Prescription medicines are safe and effective when used as directed. When they are not used as directed, it is called prescription drug abuse
- Prescription drug abuse has become a serious public safety concern. It can cause death

Medication Use

- Take the medicine exactly as directed by your health care provider
- Know if the medicine also contains acetaminophen (Tylenol™). If it does you should not take extra acetaminophen (Tylenol™). Ask your health care provider what additional medicines you may take if needed.
- Read the instructions that come with the medicine
- Do not drink alcohol while taking your prescription medicines
- Do not share your prescriptions with other people

Safe Storage

- Store the medicine in the labeled pill bottle and do not switch containers.
- If you have children, consider storing your medicine in a locked container or cupboard to prevent accidental poisoning

Disposal

- If you have additional medicine after taking the prescribed amount, it should be thrown away immediately
- Follow disposal instructions that come with the medicine. Ask your pharmacist if you have questions
- Scratch out all identifying information on the prescription label so it cannot be read.
- Before throwing the medicine in the regular garbage:
  - If the medicine is a liquid, put it in a sealed bag or container to prevent leaking
  - If the medicine is a pill, mix them in with things such as coffee grounds or cat litter in a sealed bag or container so children and pets will not want to pick them out
  - Some communities may offer prescription medicine take-back programs for the public

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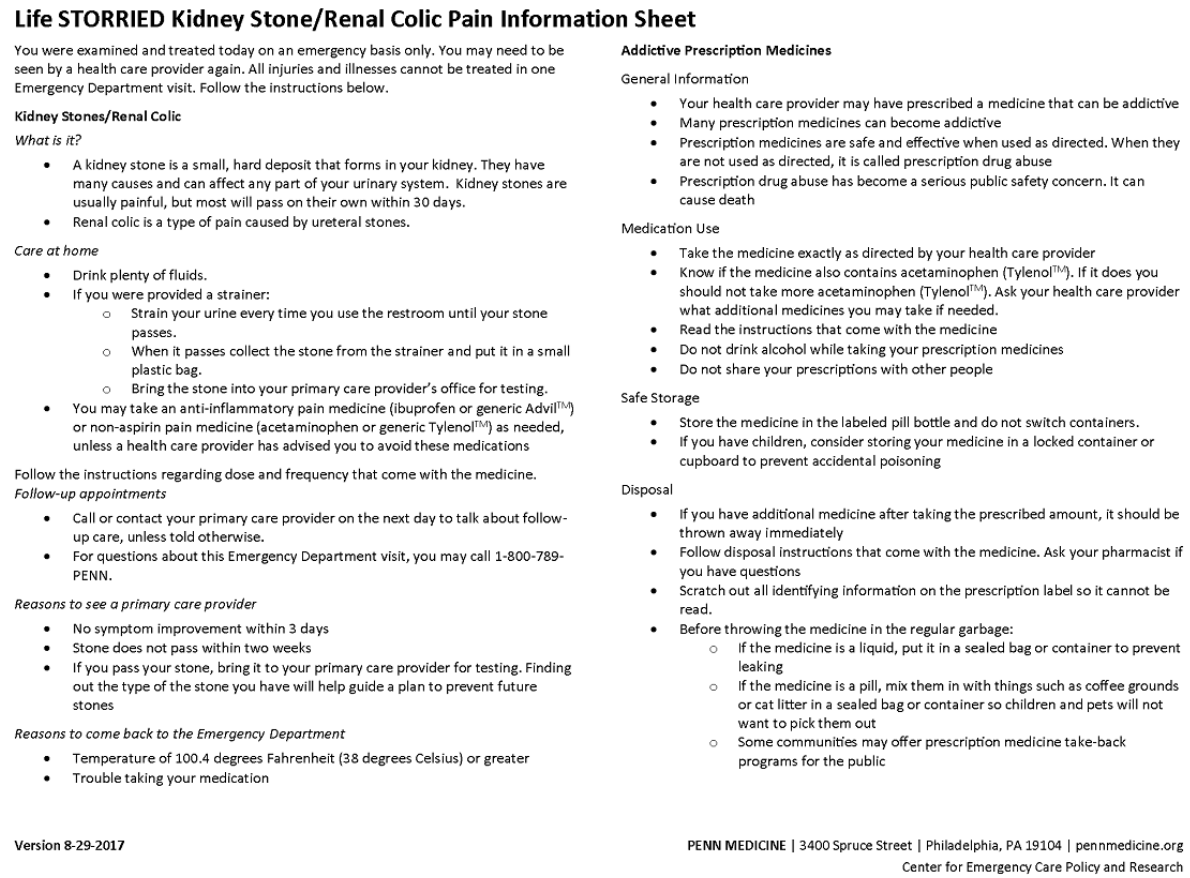
Figure 2. General risk comparator kidney stone pain information sheet for the Life STORRIED (Life Stories for Opioid Risk Reduction in the ED [emergency department]) study.



Life STORRIED Kidney Stone/Renal Colic Pain Information Sheet

You were examined and treated today on an emergency basis only. You may need to be seen by a health care provider again. All injuries and illnesses cannot be treated in one Emergency Department visit. Follow the instructions below.

Kidney Stones/Renal Colic

What is it?

- A kidney stone is a small, hard deposit that forms in your kidney. They have many causes and can affect any part of your urinary system. Kidney stones are usually painful, but most will pass on their own within 30 days.
- Renal colic is a type of pain caused by ureteral stones.

Care at home

- Drink plenty of fluids.
- If you were provided a strainer:
  - Strain your urine every time you use the restroom until your stone passes.
  - When it passes collect the stone from the strainer and put it in a small plastic bag.
  - Bring the stone into your primary care provider's office for testing.
- You may take an anti-inflammatory pain medicine (ibuprofen or generic Advil™) or non-aspirin pain medicine (acetaminophen or generic Tylenol™) as needed, unless a health care provider has advised you to avoid these medications

Follow the instructions regarding dose and frequency that come with the medicine.

Follow-up appointments

- Call or contact your primary care provider on the next day to talk about follow-up care, unless told otherwise.
- For questions about this Emergency Department visit, you may call 1-800-789-PENN.

Reasons to see a primary care provider

- No symptom improvement within 3 days
- Stone does not pass within two weeks
- If you pass your stone, bring it to your primary care provider for testing. Finding out the type of the stone you have will help guide a plan to prevent future stones

Reasons to come back to the Emergency Department

- Temperature of 100.4 degrees Fahrenheit (38 degrees Celsius) or greater
- Trouble taking your medication

Addictive Prescription Medicines

General Information

- Your health care provider may have prescribed a medicine that can be addictive
- Many prescription medicines can become addictive
- Prescription medicines are safe and effective when used as directed. When they are not used as directed, it is called prescription drug abuse
- Prescription drug abuse has become a serious public safety concern. It can cause death

Medication Use

- Take the medicine exactly as directed by your health care provider
- Know if the medicine also contains acetaminophen (Tylenol™). If it does you should not take more acetaminophen (Tylenol™). Ask your health care provider what additional medicines you may take if needed.
- Read the instructions that come with the medicine
- Do not drink alcohol while taking your prescription medicines
- Do not share your prescriptions with other people

Safe Storage

- Store the medicine in the labeled pill bottle and do not switch containers.
- If you have children, consider storing your medicine in a locked container or cupboard to prevent accidental poisoning

Disposal

- If you have additional medicine after taking the prescribed amount, it should be thrown away immediately
- Follow disposal instructions that come with the medicine. Ask your pharmacist if you have questions
- Scratch out all identifying information on the prescription label so it cannot be read.
- Before throwing the medicine in the regular garbage:
  - If the medicine is a liquid, put it in a sealed bag or container to prevent leaking
  - If the medicine is a pill, mix them in with things such as coffee grounds or cat litter in a sealed bag or container so children and pets will not want to pick them out
  - Some communities may offer prescription medicine take-back programs for the public

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Figure 3. Opioid Risk Tool showing patient is At Risk. Life STORRIED: Life Stories for Opioid Risk Reduction in the ED (emergency department) study.

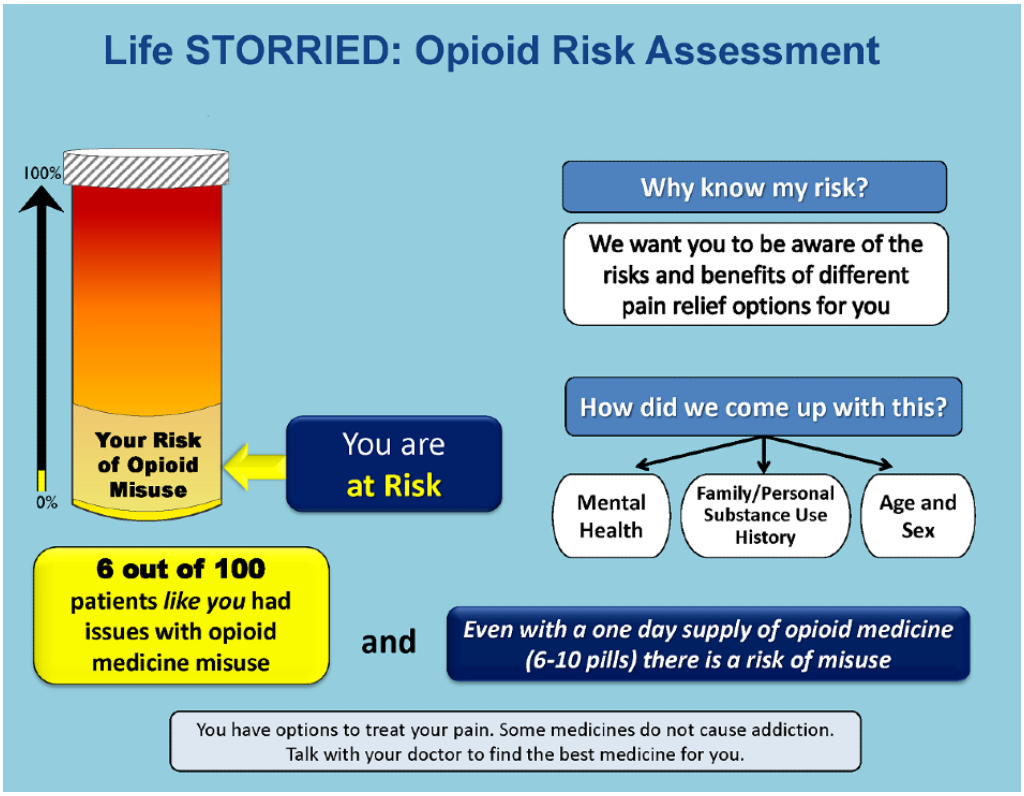


Figure 4. Opioid Risk Tool showing patient is At High Risk. Life STORRIED: Life Stories for Opioid Risk Reduction in the ED (emergency department) study.

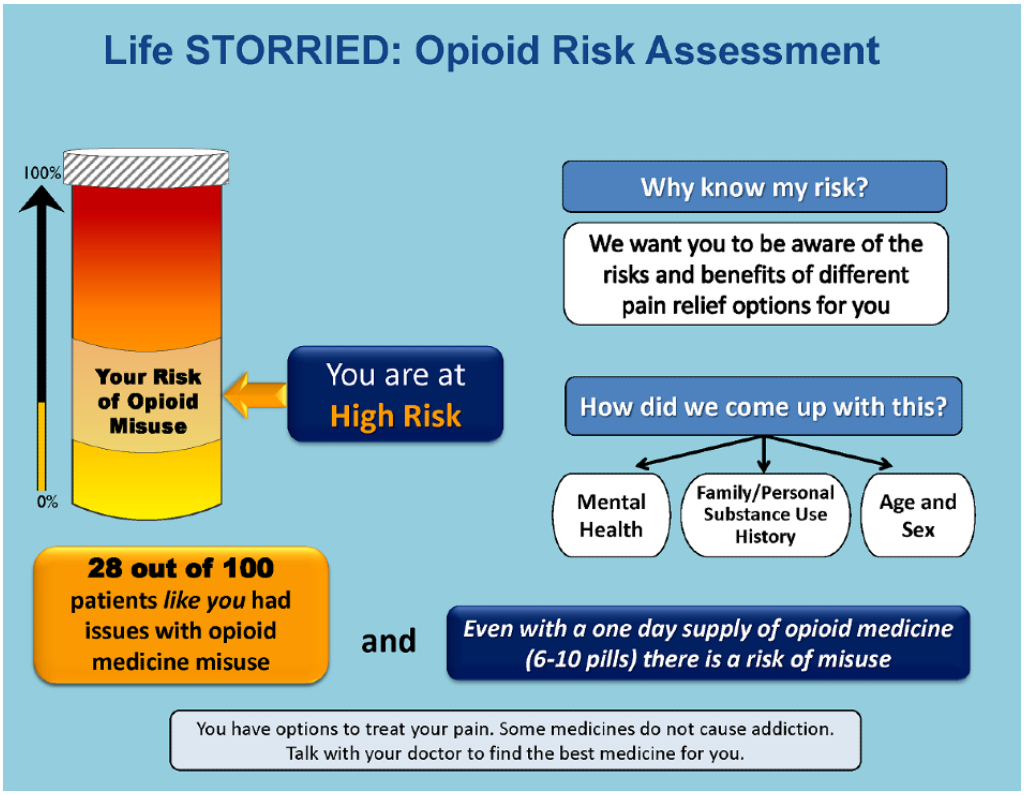


Figure 5. Opioid Risk Tool showing patient is At Highest Risk. Life STORRIED: Life Stories for Opioid Risk Reduction in the ED (emergency department) study.

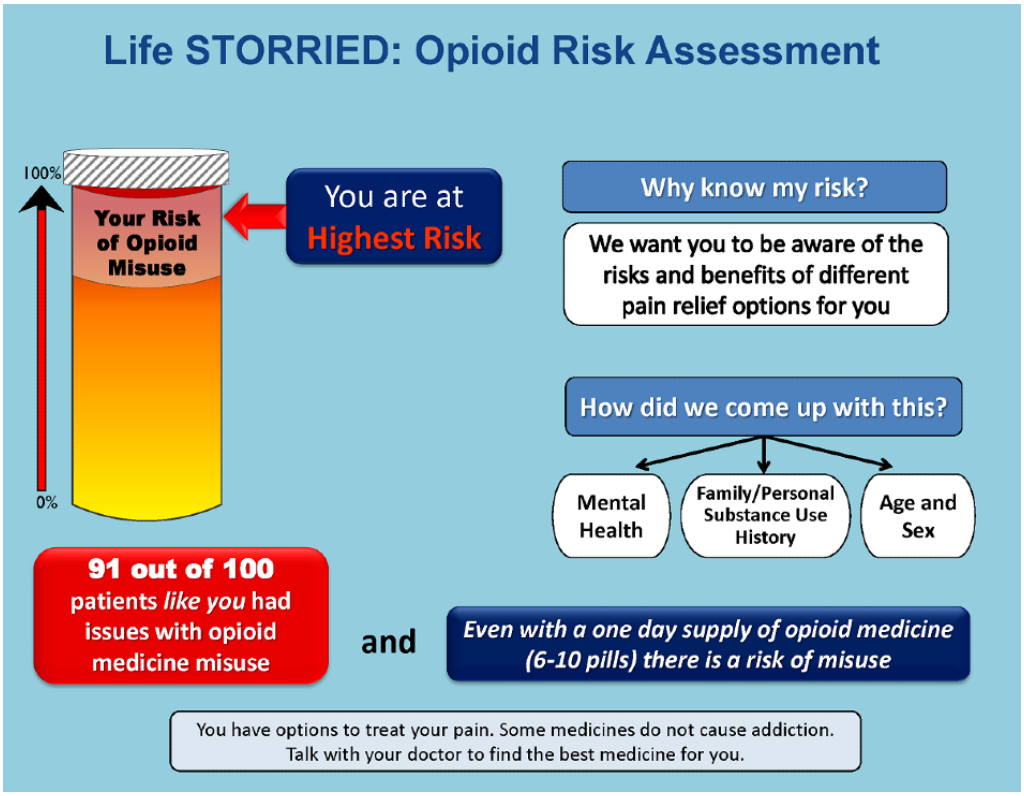


Figure 6. Narrative videos.

Jeff's Story: https://youtu.be/LF0PIpUfqXs

Mike's Story: https://youtu.be/Nrau7oVc4d0

Sharon's Story: https://youtu.be/6njJNPm7cLA

Dena's Story: https://youtu.be/J24WwqXAceA

Elise's Story: https://youtu.be/IxDii1VNWv0

Linda's Story: https://youtu.be/xKUFio61TWI

Paul's Story: https://youtu.be/3XlA4vc7BME

Rachel's Story: https://youtu.be/SApSwyOE3Fw

Patients are stratified by complaint (ie, renal colic or back and neck pain) and hospital center (ie, the University of Pennsylvania, Northwell Health, the Mayo Clinic, or the University of Alabama at Birmingham [UAB]). Electronic consent and randomization within strata and hospital centers occur automatically through a password-protected, web-based data collection platform for behaviorally oriented randomized clinical trials; this occurs during the enrollment process [31] using computer-generated random numbers. All outcome data are collected through the web-based platform, which is a secure, electronic database accessible only to researchers.

Probabilistic Risk Tool Development

The PRT was developed by the research team based on the validated ORT survey. The ORT was designed to assess risk of opioid dependency for patients for whom an opioid pain relief prescription was being considered in outpatient settings. The ORT considers multiple clinical and experiential factors in assessing risk of opioid dependency and reports risk on a scale of 0-26, divided into three probabilistic categories of risk for opioid misuse. In validation studies, 6% of patients in the lower-risk category (score 0-3) developed substance use disorder (SUD), 28% of patients in the moderate-risk category (score 4-7) developed SUD, and 91% of patients in the high-risk category (score 8-26) developed SUD [22]. It should be noted that the ORT was never specifically validated in the emergency department setting. Through an iterative process that drew on the team's expertise in patient-provider communication and shared decision making, a visual aid of the ORT results was developed. The team partnered with experts in patient communication to create a tool that was easy to interpret and leveraged best practices of risk communication in settings where literacy and numeracy would vary [32]. Using an iterative process, we developed a visual tool that uses each patient's assessed ORT score to demonstrate an absolute number and an overall risk category displayed on a visual scale; this was developed in collaboration with patient stakeholders, experts in the fields of patient education and communication, and clinical educators. Tool development followed best practices for decision aid development as defined by the International Patient Decision Aid Standards [33]. The prototype was also informed by our team's previous work to identify patient views [34] and provider views [35,36] on this topic. The probabilities described above are expressed with consistent denominators of 100 (ie, 6/100, 28/100, or 91/100). A color-coded visual thermometer is used to deliver information in a comparative fashion that accounts for lower levels of health literacy and numeracy. Aware that no group, including the one at the lowest risk, had less than a 6% risk of aberrant behavior, the color green was eliminated from the thermometer so that the revised spectrum would go from yellow to orange to red as the patient's individual risk increased. A probability of 6/100 corresponds to a yellow category of *At Risk*, 28/100 corresponds to an orange category of *At High Risk*, and 91/100 corresponds to a red

category of *At Highest Risk*. A total of six iterations that included multiple rounds of meetings as a full study team, elicitation of patient investigator input, revision of the tool, and elicitation of further input was performed. The PRT was then piloted for 2 days in the emergency department for patients in acute pain, in order to seek feedback from patients, providers, and staff, and further refinements were made.

Narrative Videos

To develop the narrative videos, the research team recruited patients and caregivers with lived experiences to record their stories. Professional videographers edited the videos for clarity and salience. The team then tested the videos through an iterative process with a core group of patient investigators and community stakeholders to maximize factors such as identification with characters, perceived realism, normative values, and reinforcement. Each narrative is a 1-3-minute, first-person, interview-based vignette of a patient or caregiver sharing personal perspectives and experiences of acute pain and opioid use and misuse. Together, the eight narrative videos feature patients of diverse backgrounds and risk levels to offer a balanced, varied commentary. Originally, an earlier version of the narratives displayed individual risk scores and was designed to align closely with known mechanisms of narrative persuasion, such as transportation, by using scripted stories derived from real experiences and narrated by professional actors. Ultimately, because the investigation team and patient advisors felt that these stories were overly scripted and not realistic, we chose to film real patients with real stories sharing their stories. These stories were real but did not align perfectly to any specific risk scoring system or any specific mechanism of narrative persuasion (see Table 1 [23-30]).

Table 1. Descriptions of the narrative videos.

Name of narrator	Video description
Paul [23]	Paul misused opioids after being prescribed OxyContin for a painful condition.
Linda [24]	Linda, a nurse, misused opioids after surgery for cancer and migraine headaches.
Elise [25]	Elise lost her young daughter to a heroin overdose after being introduced to opioids by friends.
Mike [26]	Mike prefers to avoid opioids due to his family history of addiction.
Jeff [27]	Jeff, a nurse, misused opioids after being prescribed them for a broken arm.
Dena [28]	Dena's doctor, knowing her history of addiction, helped her to avoid misusing opioids after a painful cancer surgery.
Sharon [29]	Sharon experiences chronic pain and takes opioids daily to cope with the pain.
Rachel [30]	Rachel lost her brother to an opioid overdose after he was introduced to them by a friend.

Study Overview and Objective

The primary objective of this study is to determine whether risk-informed communication with or without a narrative-enhanced tool can improve functional outcomes and patient-centered outcomes in the domains of knowledge and opioid use. Specifically, the study will measure the effectiveness of different risk communication strategies using the following outcomes: risk awareness as well as opioid and treatment preferences for fewer opioids, particularly among those at higher risk for addiction. See Table 2 for a full list of primary and secondary measures, response types, collection points, and their relevance to patients and other stakeholders.

We hypothesize that patients receiving narrative-enhanced risk communication will demonstrate greater knowledge as determined by awareness of risk for opioid dependency and will request and take fewer opioids for fewer days, while achieving the same degree of pain relief and improved functional status, as compared to study patients receiving only a generalized risk information sheet or information sheet plus an individualized, visual probabilistic risk communication tool.

Table 2. Outcomes and covariates and their measurement details.

Outcomes and covariates	Measure	Collection point	Response type or analysis	Statistical test
Primary patient-reported outcomes				
Risk awareness and recall	Opioid Risk Tool and risk assessment recall	Baseline, day 14, and at 3 months	Ordinal (three options) for baseline risk and risk recall	Cohen weighted kappa (within treatment arm) and χ^2 tests (crude agreement)
Self-reported opioid use	*Yes* or *no* if taking opioids	Days 1, 2, 4-6, and 14 and at 3 months	Dichotomous (*yes* or *no*)	Zero-inflated negative binomial or zero-inflated Poisson models
Patient-reported preference for pain relief	Patient pain relief preference survey	Baseline	Five options for patient-reported pain relief preference	Cochran-Armitage χ^2 test for trend
Agreement on pain treatment between patient preference and provider decision	Patient preference vs electronic medical record documentation		Five options for patient-reported pain preference and concordance with provider decision	Cohen weighted kappa, intraclass correlation coefficient, Bland-Altman plots (within treatment arm), and χ^2 tests (crude agreement)
Secondary patient-reported outcomes				
Days to no opioid use	Number of pain medications taken daily	Days 1,2, 4-6, and 14 and at 3 months	Continuous (number of pills of each type)	Kaplan Meier and proportional hazards (time to full functionality)
Functional status	Back Pain Functional Scale and the 20-Item Short Form Survey from the Medical Outcomes Study	Days 1, 7, and 14 and at 3 months	Likert scale (0-10) and composite score for five items (0-50)	Kaplan Meier, proportional hazards (time to full functionality), and random-effects mixed model to measure clinically important changes in functionality
Satisfaction with pain treatment	American Pain Society Patient Outcome Questionnaire	Baseline; days 1, 7, and 14; and at 3 months	Likert scale (1-6) and dichotomous (*satisfied* vs *not satisfied*)	χ^2 tests, Mantel-Haenszel summary statistics, and general linear model with log-linear link
Trust in provider	Trust in Physician Scale	Day 7	Likert scale (1-5) and composite score for 11 items (11-55)	Analysis of variance or Kruskal-Wallis test
Follow-up visits for pain	Self-report of additional provider visits	Day 14 and at 3 months	Dichotomous (*yes* or *no* visits; *yes* or *no* provide pain pills)	χ^2 test and general linear model with log-linear link
Patient-reported measure of shared decision making	CollaboRATE	Day 1	Likert scale (1-10)	Analysis of variance or Kruskal-Wallis test
Opioid misuse	Current Opioid Misuse Measure	At 3 months	Dichotomous score (≥*9* vs <*9*)	χ^2 test and general linear model with log-linear link
Covariates (subgroup analyses)				
Demographics	GENACIS[a] and BRFSS[b] 2011	Baseline	Varies by question	N/A[c]
Overall health	Self-rated health	Baseline and at 3 months	Likert scale (1-5)	N/A
Medical condition (back vs renal colic)	ICD-9[d] codes and primary complaint	Baseline	ICD-9 codes	N/A
Medical history	Electronic health record	Baseline	ICD-9 codes	N/A
Risk for opioid dependency	Opioid Risk Tool	Baseline	Continuous score (0-26) risk level (*high*, *medium*, or *low*)	N/A

[a]GENACIS: Gender, Alcohol, and Culture: An International Study.

[b]BRFSS: Behavioral Risk Factor Surveillance System.

[c]N/A: not applicable. As these were not outcomes, we do not report statistical tests; these are listed as covariates.

[d]ICD-9: International Classification of Diseases, Ninth Revision.

Setting

Patients are recruited from acute care settings (ie, emergency department or observation units) in four US academic hospital centers: (1) the University of Pennsylvania in Philadelphia, Pennsylvania, located on the east coast with an urban patient population, (2) Northwell Health (ie, Long Island Jewish Hospital and North Shore Hospital) in Long Island, New York, located on the east coast with a suburban patient population, (3) the Mayo Clinic in Rochester, Minnesota, located in the Midwest with a diverse rural, suburban, and small-city patient population, and (4) the UAB, Alabama, located in the Southeast with an urban patient population. These centers were selected to capture geographically and ethnically diverse patient populations and clinical practices.

Sample Population and Recruitment

Our sample population includes patients presenting to participating study sites with a chief complaint suggestive of acute renal colic or musculoskeletal neck or back pain. A trained project manager, research coordinator, or research associate identifies eligible patients based on chart review and collaborates with the treating clinician to confirm patient eligibility for the study. Patients are concurrently enrolled at all participating study sites 5-7 days per week, whenever a trained enroller is available.

Selection of Participants

The study inclusion and exclusion criteria are listed in Textbox 1.

Textbox 1. Participant inclusion and exclusion criteria.

Inclusion criteria:

- Patients 18-70 years of age presenting to an acute care setting AND
- Chief complaint indicative of acute neck, back, and/or flank pain OR uncomplicated kidney stones AND
- Capable of providing informed consent AND
- English-speaking OR Spanish-speaking with English comprehension AND
- Able to access a smartphone or email account regularly AND
- The treating clinician anticipates discharge within 24 hours with a diagnosis of renal calculi or musculoskeletal back pain

Exclusion criteria:

- Pregnancy
- In police custody
- Under the influence of illicit drugs or alcohol
- Mentally or cognitively unstable
- Suicidal
- Homicidal OR
- Unable to take opioids or nonsteroidal anti-inflammatory drugs (NSAIDs) for any reason

Additionally, patients who display aberrant drug use behavior, as determined by the lead provider, or have used opioid medications in the past 30 days—excluding opioids taken for the current condition within 48 hours of this acute care visit—are ineligible. Patients with a known history of chronic kidney disease (glomerular filtration rate <60) are also ineligible, because they may not be able to take nonsteroidal anti-inflammatory drugs (NSAIDs).

Baseline Enrollment: Day 0

After providing informed consent, participants answer questions from a series of surveys, including the following: (1) an informational profile of demographic data (ie, gender, race, ethnicity, and education level) [37-39], (2) the Revised American Pain Society Patient Outcome Questionnaire [40], (3) the 20-Item Short Form Survey from the Medical Outcomes Study (MOS-20) [41], (4) a tobacco use survey [38], (5) the ORT [22], (6) the Screener and Opioid Assessment for Patients with Pain-Revised [42], and (7) a pain relief preference survey. Participant responses to survey questions are recorded in real time on a secure, password-protected iPad or tablet owned by the study. Study staff will administer surveys (1) through (3) and (7), whereas participants will complete surveys (4) through (6) directly on the study tablet computer due to the sensitive nature of these questions.

All participants are given—in addition to standard institution-specific discharge instructions—a generalized, fact-based risk information sheet for renal colic or neck and back pain, based on chief complaint. This information sheet was developed by consensus among the study team, including clinicians, patients, and nurse educators. During enrollment, patients are given 3 minutes to familiarize themselves with the risk information sheet and ask questions to study staff.

Regarding the ORT, for participants randomized into either intervention arm, the tablet computer will display one of three ORT images—*At Risk*, *At High Risk*, or *At Highest Risk* for opioid misuse—based on participant responses to the ORT survey (see Figures 3-5).

Regarding video narratives, for participants randomized to the narrative-enhanced PRT arm, also displayed is a menu with a choice of eight video narratives (see Figure 6 and Table 1). The narratives are displayed in a menu format on a tablet computer and participants can watch any story by selecting the picture of the storyteller. The participants may view as many videos as desired. Participants are provided the option of using headphones, and, when possible, study staff exit the room for privacy until the patient has completed viewing the videos.

Participant Follow-Up: Days 1-7, Day 14, and 3 Months

Outcomes were decided through a process that included iterative discussions with the entire investigative team, including patient investigators, as well as feedback from the study sponsor peer review. On days 1 through 7 and 14 after enrollment, the study portal sends participants automated email or text messages containing links to secure, online follow-up surveys. These brief surveys collect information on patient satisfaction and outlook [40], pain management strategies and functional outcomes, behavioral and functional characteristics [41,43], medication use behaviors [44], quality of life [41], health literacy [45], and health numeracy [46]. Patients randomized to the video narrative–enhanced PRT arm also receive messages encouraging them to continue to view the eight video narratives through an individualized portal. A total of 3 months after enrollment, the portal will send participants automated email or text messages containing a link to a secure final follow-up survey of the above attributes, as well as recall of opioid risk level and/or viewing of video narratives for patients randomized to the corresponding intervention arms.

Text and email reminders are used to promote continuous engagement and follow-up among study participants. Small cash incentives are used to maximize retention and promote follow-up. All subjects are eligible to receive up to US $84 for completing enrollment and follow-up surveys. Because of lower-than-expected response rates to the day-14 follow-up at the beginning of the study, the total eligible incentive was increased on January 15, 2018, from US $50 to US $84 to improve response rates and minimize study attrition. For the survey at 3 months, if the subjects do not respond to the electronic reminders, research staff will call the participants to remind them to complete survey; if necessary, they will conduct the survey by telephone.

Analysis

Overview

Standard statistical tests (ie, χ^2, analysis of variance [ANOVA], or Kruskal-Wallis tests) will be performed to determine outcome distributions and whether patients differ with regard to demographics in the three study groups. To determine differences in knowledge of risk for opioid dependency between NERT and PRT groups, agreement between individual risk as measured by the ORT and recall of risk at 14 days and 3 months will be classified as concordant or discordant for the risk category. Using these dichotomous outcomes, logistic regression models that include treatment arm, demographics (ie, age, gender, and ethnicity), and risk category will be developed. This will allow for the comparison of NERT and PRT treatment groups while adjusting for potential confounders. To test the hypothesis that patients in the NERT group request and take significantly less morphine equivalents than do patients in the PRT or control groups, the primary analytic technique will be a Poisson (log-linear) regression or a zero-inflated negative binomial regression [47]. If necessary, all models will be adjusted for baseline pain level, condition, observation versus discharge status, and any complications, as well as possible interactions or confounders, such as age, gender, race, education, employment, insurance, income (ie, socioeconomic status), and marital or relationship status. To assess differences in number of days to cessation of opioid use, among those who reported taking opioids from any source, and time to return to functional status over the 3-month study period among the three treatment arms, we will utilize Kaplan-Meier curves and Cox proportional-hazard models. The log-rank test will be used to assess differences in rate of cessation of opioid use and rate of return to functionality between the three treatment groups. Additionally, at the 3-month survey time point, functionality will be assessed with MOS-20 scales [41]. For this analysis, a 2-way ANOVA, with group and condition as main effects, will be used. The number of narratives viewed and where the viewing occurs (ie, in the emergency department or at home) will be assessed.

Sample Size and Power Calculation

Sample size was calculated based on the outcome deemed to require the most participants to demonstrate a meaningful effect of the intervention. To determine the number of patients needed in each group for sufficient sample size, we first considered one of the outcomes measured: number of days to no opioids. The final sample size was based on the number of days (ie, rate) to no opioid use, as this was presumed to require the largest sample size to detect a clinically meaningful effect between PRT and NERT groups. Using a 2-sided log-rank test with an overall predicted starting sample size of 1100 subjects, which increased to 1300 midstudy due to lower-than-expected response rates at day 14, achieves 80% power at a .05 significance level to detect a hazard ratio of 0.46 when the proportion not taking opioids at 14 days in the PRT group is 0.70 (an effect size as small as 15%) and the loss to follow-up is 25%-30%. This sample size was also designed to allow for stratified analyses by condition, should the responses to the interventions between conditions not be homogenous. The general risk comparator group was included in the sample size calculation as well, should we find no difference between NERT and PRT groups. Using an effect size of 10%-15% difference in proportions still using opioids, which we considered to be clinically meaningful and also obtainable based on our pilot data, and conservatively estimating a 20%-25% loss to follow-up in this group, we determined we would have sufficient power to evaluate a 10% difference, assuming that 95% and 85% of participants would no longer be taking opioids at 2 weeks in the NERT group versus the general risk comparator group, respectively. If a participant no longer responds to follow-up questions, he or she will be evaluated with the data collected on the earlier collection days of the study. Imputation will be used for key variables, with sensitivity analysis, when missing data are determined to be

likely to be missing at random and are equally distributed across the intervention arms.

Limitations

An important limitation is the lack of standardization of the definition of aberrant drug use that was used as an exclusion criterion. During enrollment, the emergency department provider determined whether they believed each potential participant demonstrated aberrant drug use. Whether they used objective or subjective evidence was not predetermined. This exclusion criterion, as well as the exclusion of patients with prior use, was made in response to sponsor reviewer concerns that these tools would be of little use for patients who are "doctor shopping" or who already have an opioid use disorder.

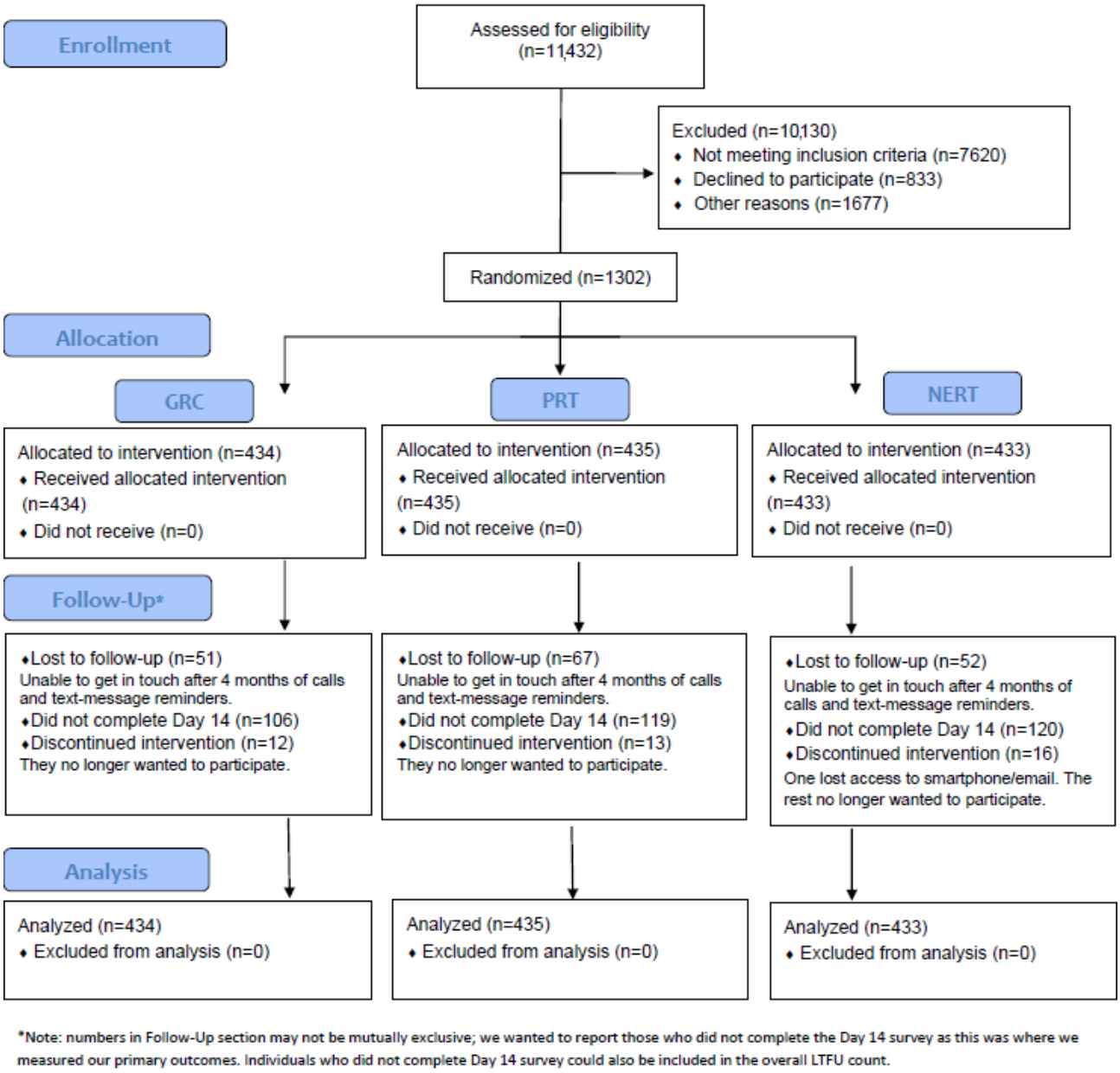
The ORT has previously been tested in the emergency department but not fully validated. It was designed for primary care settings, among which acute pain for back and kidney stone pain are common complaints. It remains an easy-to-implement tool that could be stratified in a way that the visual and risk tools could be tested.

Patients were provided with the possibility of repeat electronic exposure to the narrative intervention but not their specific risk score display. However, the risk thermometer was provided as a hard copy to patients on discharge, with the possibility of repeat exposure. Because risk recall was a primary outcome, we did not wish patients to look up their score in real time as an answer to the risk recall question (ie, social desirability). Home viewing of the narratives was deemed an important outcome and part of the intervention as they were generalized and could be shared and viewed; however, this required some additional time that could not be achieved at the point of care during a busy emergency department visit.

Results

The study was funded in September 2016. It was approved by the University of Pennsylvania IRB on January 18, 2017. In 2018, the UAB site was added to the study and additional local IRB approval was required for this site only. The UAB IRB approved the study on July 27, 2018. Data collection commenced on October 24, 2018. On February 27, 2019, without unblinding the data, the original study sample size was expanded from 1100 to 1300, based on follow-up survey completion rates that were lower than expected. This increase was implemented in order to maintain the original power analysis for days to no opioid use. On August 7, 2019, the final participant was enrolled, and on November 19, 2019, the final data collection survey was obtained (see Figure 7 for the Consolidated Standards Of Reporting Trials [CONSORT] diagram). Analysis is underway. The mean age of the participants was 40 years (SD 14), 692 out of 1302 (53.15%) were female, 556 out of 1302 (42.70%) were White, 498 out of 1302 (38.25%) were Black, 1002 out of 1302 (76.96%) had back pain, and 334 out of 1302 (25.65%) were at medium or high risk. Out of 1302 participants, 343 (26.34%) were prescribed opioids at the original visit. Age, race, gender, and ORT scores were equally distributed across arms.

Figure 7. The Consolidated Standards Of Reporting Trials (CONSORT) diagram for the Life STORRIED (Life Stories for Opioid Risk Reduction in the ED [emergency department]) study. GRC: general risk comparator; LTFU: long-term follow-up; NERT: narrative-enhanced risk tool; PRT: probabilistic risk tool.



Discussion

In this national multicenter randomized clinical trial, 1302 people with kidney stone or back pain were randomized to receive one of three communication interventions regarding pain control after emergency department discharge; 21% were prescribed opioids. Analysis is underway to determine the effect of the interventions on knowledge, opioid use and preference, and patient-provider alignment in decision making.

In the United States, prescription opioid misuse affects nearly 2 million people [48]. Researchers have sought to validate opioid risk tools for individual patients, but have not explored how these risk tools work or how they can be used from the patient's perspective [49,50]. This manuscript describes the Life STORRIED study protocol used to implement a multicenter randomized clinical trial for evaluating the clinical potential of different risk communication strategies, with the goal of optimizing patient and provider decision making about opioid use. This study is significant to patients and providers for at least two reasons. First, achieving adequate relief from acute pain while balancing addiction risks and side effects of prescription opioids is a major challenge for patients and providers. Acute pain management contributes largely to the US crisis of prescription opioid misuse, which often begins with prescriptions for acute pain and is costly and harmful to families, communities, and society as a whole. Second, patients are

frequently exposed to either under- or overtreatment of pain and have different risk profiles for opioid misuse, realities that may impact the appropriateness of various analgesics. The goal of this study is to provide crucial and currently lacking evidence about the value of personal narratives in communicating and managing opioid risk in acute care patients. Ultimately, this study aims to facilitate the creation of a clinically effective and cost-effective accessible tool to guide pain management decision making in acute care settings, that is, in the setting of the modern prescription opioid misuse crisis.

Acknowledgments

The study team would like to acknowledge the contributions of the courageous individuals who shared their personal stories in the process of making our narrative videos.

Conflicts of Interest

None declared.

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Abbreviations

ANOVA: analysis of variance
CONSORT: Consolidated Standards Of Reporting Trials
ED: emergency department
IRB: Institutional Review Board
Life STORRIED: Life Stories for Opioid Risk Reduction in the ED (emergency department)
MOS-20: 20-Item Short Form Survey from the Medical Outcomes Study
NERT: narrative-enhanced risk tool
NSAID: nonsteroidal anti-inflammatory drug
ORT: Opioid Risk Tool
PRT: probabilistic risk tool
SUD: substance use disorder
UAB: University of Alabama at Birmingham

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Protocol

Psychological Treatment of Low Sexual Desire in Women: Protocol for a Randomized, Waitlist-Controlled Trial of Internet-Based Cognitive Behavioral and Mindfulness-Based Treatments

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Abstract

Background: Psychological therapies are effective treatments for hypoactive sexual desire dysfunction (HSDD; formerly hypoactive sexual desire disorder), a common sexual dysfunction among women. Access to evidence-based treatments, however, remains difficult. Internet-based interventions are effective for a variety of psychological disorders and may be a promising means to close the treatment gap for HSDD.

Objective: This article describes the treatment protocol and study design of a randomized controlled trial, aiming to study the efficacy of cognitive behavioral and mindfulness-based interventions delivered via the internet for women with HSDD to a waitlist control group. Outcomes are sexual desire (primary) and sexual distress (secondary). Additional variables (eg, depression, mindfulness, rumination) will be assessed as potential moderators or mediators of treatment success.

Methods: A cognitive behavioral and a mindfulness-based self-help intervention for HSDD will be provided online. Overall, 266 women with HSDD will be recruited and assigned either to one of the intervention groups, or to a waitlist control group (2:2:1). Outcome data will be assessed at baseline, at 12 weeks, and at 6 and 12 months after randomization. Intention-to-treat and completer analyses will be conducted.

Results: We expect improvements in sexual desire and sexuality-related distress in both intervention groups compared to the waitlist control. Recruitment has begun in January 2019 and is expected to be completed in August 2021. Results will be published in 2022.

Conclusions: This study aims to contribute to the improvement and dissemination of psychological treatments for women with HSDD and to clarify whether cognitive behavioral and/or mindfulness-based treatments for HSDD are feasible and effective when delivered via the internet.

Trial Registration: ClinicalTrials.gov NCT03780751; https://clinicaltrials.gov/ct2/show/NCT03780751

International Registered Report Identifier (IRRID): DERR1-10.2196/20326

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KEYWORDS

sexual desire; sexual dysfunction; women's sexual health; cognitive behavioral therapy

Introduction

Background

A sexual dysfunction can be described as a disturbance in a person's ability to respond sexually or to experience sexual pleasure that leads to significant personal distress [1]. One of the most common sexual dysfunctions among women is a lack of sexual desire which, according to the eleventh edition of the International Classification of Diseases (ICD-11), can manifest as reduced or absent spontaneous desire (sexual thoughts or fantasies), reduced or absent responsive desire to erotic cues and stimulation, or an inability to sustain desire or interest in sexual activity once initiated [2]. If a pattern of low sexual desire is present over a period of at least several months and is associated with clinically significant distress, a hypoactive sexual desire dysfunction (HSDD; formerly hypoactive sexual desire disorder) can be diagnosed. A UK study found that among 6777 sexually active women, 34.2% experienced low desire [3]. When applying the morbidity criteria listed in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), 6.5% of women indicated low sexual desire or arousal for several months within the last year, and 0.6.% met the criteria for female sexual interest/arousal disorder [4]. Low sexual desire does not only affect women's sexual health but also has detrimental effects on their quality of life [5]. Individuals with sexual dysfunctions (including low desire) are more likely to report higher rates of sexually transmitted infections, unwanted sex, unemployment, relationship breakdown, and difficulties discussing sexuality [3]. In addition, low sexual desire is often comorbid to mental health problems such as depression and anxiety [6,7].

Treatment of Low Sexual Desire

Low sexual desire has received widespread attention from clinicians, researchers, and the lay public because of its high prevalence and its seeming resistance to treatment [8] which led to increased efforts to find a "Pink Viagra" (ie, an effective pharmacological agent) [9]. To date, flibanserin is the only drug that has received approval for treatment of low sexual desire in women in the United States and Canada. While this drug, which has pharmacological effects on serotonin and dopamine receptors [10], was being tested on patients with major depressive disorder, its positive effect on women's sexual functioning was discovered [11]. So far, 3 systematic reviews or meta-analyses have found modest positive effects on women's low sexual desire [12-14], while also acknowledging its side effects (eg, nausea, dizziness, fatigue). There has also been renewed interest in the advancement of psychological treatments for women's low sexual desire [9]. A meta-analysis found psychological interventions to be effective treatments for low sexual desire [15] and effects for symptom reduction were large compared to waitlist controls (d=0.91; 95% CI 0.38-1.45; P=.012). Furthermore, such treatments lead to medium to large increases in sexual satisfaction.

Components of Psychological Treatments for Low Sexual Desire

Psychological interventions for low desire often comprise a variety of components such as psychological and sexual education, couples exercises, guided masturbation, communication training, cognitive behavioral as well as mindfulness-based techniques [15]. Many interventions aim to educate women about their genital anatomy, psychological and physiological aspects of sexual arousal, and sexual difficulties (eg, symptoms, prevalence). Other common treatment elements are self-exploration and sensate focus. Self-exploration may include exploration of genital anatomy using a handheld mirror. Self-touch exercises aim to provide knowledge about how to elicit pleasurable sexual feelings and arousal (Brotto, Paterson, Basson, Driscoll, and Grabovac, unpublished manual, 2015 and unpublished manuscript, 2015). Sensate focus comprises gradually progressing exercises with varying degrees of touch, administered to a partner's body [16]. Exercises start with a couple taking turns at providing nonsexual touch and end with sexual intercourse.

Even supposedly specialized treatments often include a broad range of psychological methods [9]. Four modules of mindfulness-based treatment, for example, included not only mindfulness exercises but also information on sexual dysfunctions, sexual response, and female genital anatomy, supplemented by self-exploration, cognitive restructuring, and sensate focus exercises [17]. Thus, it remains unclear which of the specific treatment components are the main drivers of change and more research is needed to understand which methods and techniques are necessary and sufficient to improve women's low sexual desire.

Among the most common treatments for low desire are cognitive behavioral therapy (CBT) and mindfulness-based therapy (MBT) [15]. CBT is change oriented and is one of the most researched forms of psychotherapy. It is effective for a variety of mental health problems such as depression, anxiety disorders, and posttraumatic stress disorder [18], as well as sexual dysfunctions such as HSDD [15]. MBT is an acceptance-based approach using mindfulness, an ancient Eastern practice with roots in Buddhist meditation, defined as present-moment, nonjudgmental awareness [19], and intends to shift the focus of attention to one's body and breath. MBT has been found effective for the treatment of depression, anxiety, and stress [20]. Evidence for its effectiveness for women's sexual dysfunctions stems from a few, mostly uncontrolled, studies [17,21,22].

Internet-Based Interventions

Although many women are distressed by their lack of desire, the number of those who receive qualified, evidence-based treatment remains low [23]. Sexual dysfunctions are connected to stigma and reluctance in seeking professional help [24,25]. Furthermore, a lack of information on the treatment options prevails as well as structural barriers, such as limited access to qualified therapists. This issue could be addressed by developing and disseminating treatments that require less direct forms of contact, namely internet-based interventions. A growing body of literature suggests that interventions delivered via internet or mobile technology are feasible and effective to improve depression, anxiety [26], and even psychosis [27]. These interventions offer varying degrees of guidance ranging from self-help, user-led interventions, to regular to contact with a trained clinician. Interventions involving at least some kind of

guidance or coaching have been proven to be more effective than unguided interventions [28]. Concerning internet-based interventions for sexual dysfunctions in women, van Lankveld [29] reviewed 5 studies and found that these interventions were effective in improving sexual functioning and emotional intimacy in couples. While 2 of these studies also included women with low sexual desire [29], treatments did not focus on improvement of sexual desire but targeted a broad range of women's sexual difficulties (eg, anorgasmia, genital pain). Thus, no studies have evaluated the efficacy of internet-based CBT (I-CBT) or MBT (I-MBT) designed for the treatment low sexual desire in women.

Study Aim

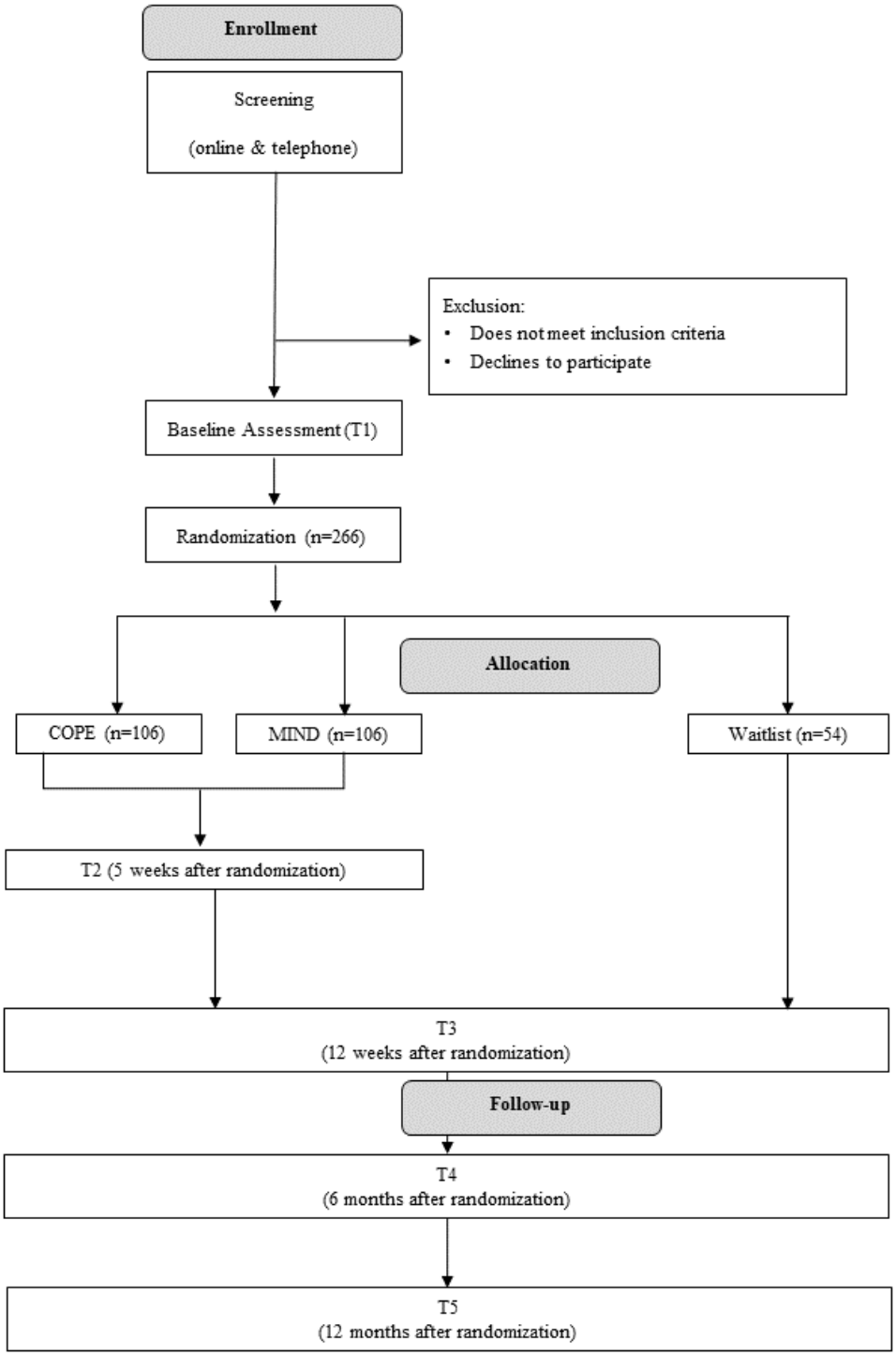
The aim of this study is to present the protocol of a randomized controlled trial (RCT) comparing 2 internet-based interventions for low sexual desire in women with HSDD to a waitlist. Hypotheses 1 and 2 are that at posttreatment (12 weeks after randomization), women receiving I-CBT or I-MBT report significantly more sexual desire (primary outcome; H1) and less sexuality-related distress (secondary outcome; H2) compared to a waitlist control condition. It is also proposed that these differences are maintained at the 6- and 12-month follow-up assessments. Differences in outcomes between I-CBT and I-MBT at the 12-week-, 6-month, and 12-month assessments are inspected on an exploratory basis. It is also explored whether improvements from pretreatment to posttreatment are dependent on treatment dosage (eg, completed modules, time spent with at-home exercises) and whether changes in proximal variables such as mindfulness or rumination mediate improvement in symptoms in either one of the treatments. Whether improvements in symptoms are predicted by changes in sexuality-related interpretations and associations assessed with computerized reaction-time paradigms (ie, Single-Target Implicit Association Test [STIAT] and Scrambled Sentences Task [SST]) is examined as well. To explore participants' perceptions of the treatments more thoroughly, qualitative telephone interviews will be conducted with 25 participants in the I-CBT and I-MBT condition, respectively.

Methods

Design

The study is an RCT of 2 internet-based treatments (ie, I-CBT and I-MBT) versus a waitlist control group. Analyses will be conducted and reported in accordance with the statement by Consolidated Standards of Reporting Trials (CONSORT) [30]. Recommendations for the reporting of psychological and eHealth interventions will be considered [31,32]. This 3-arm superiority trial with 2:2:1 allocation ratio will demonstrate whether the benefit from I-CBT or I-MBT is superior to natural remission of low desire symptoms. Outcomes will be assessed at baseline (T1), at midtreatment (T2, 5 weeks after randomization, only in active conditions), at posttreatment (T3, 12 weeks after randomization), and at 6 months (T4) and 12 months (T5) after randomization. Two computerized reaction-time paradigms will be administered at T1 and T3. Participants will receive up to 3 reminders for each assessment (after 7, 14, and 21 days). Qualitative telephone interviews with active participants will be conducted at T3. For an overview of participant flow, see Figure 1.

Figure 1. Participant recruitment flowchart.



Participants

Inclusion and Exclusion Criteria

Inclusion criteria are being 18 years or older; completion of the informed consent form; female gender; being able to read, write, and speak German; and meeting ICD-11 criteria for HSDD. Exclusion criteria are being pregnant, ongoing treatment for any sexual dysfunction or plans to enter such treatment, symptoms of a physical condition that might interfere with study participation (eg, cancer, multiple sclerosis), current substance use disorder, current or lifetime schizophrenia spectrum or other psychotic disorders, and significant relationship discord or violence. As sexual dysfunctions show high rates of comorbidity with other mental health issues such as anxiety or affective disorders [7,33], women experiencing mild to moderate symptoms of other mental disorders are not excluded automatically. Rather, symptoms of a mental disorder (eg, eating disorders, obsessive-compulsive disorder, posttraumatic stress

disorder, major depression, bipolar disorder) that might interfere with participation (ie, might make it too burdensome for individuals to participate in data assessments) are assessed during screening. Women whose low desire may be fully attributable to pain during sexual intercourse are also not included. Inclusion and exclusion criteria will be assessed in a 2-step process consisting of an online screening followed by an in-depth telephone interview with a clinical psychologist.

Procedure

In order to recruit a diverse sample of women of different ages, sexual orientations, and ethnicities, a variety of recruitment strategies will be employed. Women can learn about the study by visiting a designated study website and associated pages on social networks, articles in local and nationwide media publications (eg, magazines, newspapers), online discussion boards, and flyers at specialized counseling agencies/sites, general practitioners, and gynecologists.

Recruitment and study enrollment will follow a stepwise procedure. Potential participants will be invited to complete an online questionnaire assessing inclusion and exclusion criteria. Individuals not meeting the study criteria (eg, male gender, no sexual concerns, or minors) will be informed and, if needed, be referred to other resources (eg, their physician, counseling services). For all other individuals, an in-depth telephone interview with a clinical psychologist will be scheduled to evaluate eligibility. If an individual is eligible, she will receive an invitation to an internet-based questionnaire. Women who complete this baseline assessment and who provide informed consent electronically will be enrolled.

Randomization

Enrolled participants will be randomly assigned to 1 of the 3 conditions. To maximize the power of the study to detect differences between active and control conditions, quotas are applied to allocate 40% of participants to each of the active treatments and 20% to the waitlist. A stratification procedure will be applied to balance relationship status (partner vs no partner) and age (younger than 30 years vs 31 years and older). These variables were selected based on their known effect on sexual desire [34-36]. An internet-based randomization tool will be used by a trained research assistant not involved in the recruitment, screening, or treatment of participants [37]. The clinical psychologist conducting the diagnostic interviews will not be involved in the randomization process but will be informed about the assigned condition after its completion. Block randomization with varying block-sizes will be applied. Participants will be informed about their assigned condition. Participants in the active conditions will gain immediate access to the respective program. Participants assigned to waitlist will receive access to a program of their choice (ie, I-CBT or I-MBT) 6 months after randomization.

Power Analysis

Sample size was determined based on an a priori power analysis and practical considerations. Psychological therapies for sexual dysfunctions in women yield large effects for symptom improvement compared to waitlist controls (d≈0.9) [15,29]. To use a conservative estimate, a medium effect of d=0.6 was expected for both active conditions compared to the waitlist (unpaired t test two-sided, α=.025, 1–β=80%, allocation rate 2/1). In addition, a postsample of 81 women for each of the 2 active conditions would yield statistical power of 60%, 71%, and 81% to detect differences of d=0.35, 0.40, or 0.45, respectively. Although this study is not sufficiently powered to detect smaller differences in efficacy between I-CBT and I-MBT, it will still provide first estimates that may be useful for future studies. As internet-based interventions commonly suffer from relatively high attrition rates, a 30% loss at postassessment analysis is expected. Based on these considerations, a total of 266 women will be enrolled in the study.

Interventions

Structure and Content of Both Interventions

The study introduces 2 internet-based, guided, self-help interventions for low sexual desire in women. To allow for a clear communication with participants, the I-CBT and I-MBT programs are entitled COPE and MIND, respectively. COPE and MIND consist of 8 modules each; women are encouraged to complete 1 module per week. Four weeks after completion of Module 8, participants will gain access to an additional booster module. For a more detailed overview of the modules, see Table 1. Modules are designed to be completed by most participants within 45-60 minutes. Participants are free to take additional time for completion, if needed. As an optional feature, participants are invited to keep an internet-based daily diary of their mood, level of sexual desire, and the time spent with at-home exercises each day. This diary can be accessed via a corresponding smartphone app. Both COPE and MIND have been developed based on existing face-to-face group treatments for low sexual desire (Brotto, Paterson, Basson, Driscoll, and Grabovac, unpublished data, 2015) as well as an internet-based intervention for women with genito-pelvic pain/penetration disorder [38]. If participants fail to log in to the platform for 7 consecutive days, they will receive up to 4 reminders (after 7, 14, 21, and approximately 30 days) by their eCoach and the study coordinator.

In each module, participants receive new information and are introduced to new at-home exercises to be completed between modules. Self-exploration (Modules 2-4) and sensate focus exercises (Modules 6-8) as well as information on the prevalence of sexual dysfunctions, genital anatomy, and sexual response (Modules 1-3) are included in both COPE and MIND. In Module 2, participants will be introduced to the circular sexual response model as proposed by Basson [39] and in each of the following modules, different parts of the cycle will be presented. This model proposes that women with low desire tend to enter sexual situations from a state of neutrality and, if context and stimulation are adequate, may develop sexual arousal and responsive sexual desire during the course of a (pleasing) sexual encounter. (For more information, see Basson [40]). Participants are given the opportunity to work with their sexual response cycle, to reflect on their own situation (eg, to identify contexts they find sexually arousing, to explore reasons for sexual activity), and to develop strategies to improve their sexual experiences.

Table 1. Content of the modules.

Module	Content		
	MIND	COPE	Sex therapy (for both interventions)
1	Introduction to mindfulness	Introduction to cognitive behavioral model and body image	Psychoeducation, information about psychological and physiological aspects of sexual response
2	Being present in the moment: Formal and informal mindfulness	Sexual myths	Self-exploration, body exposure
3	Bodily sensations, sitting meditation	Thought protocol, cognitive distortions	Self-exploration, body exposure
4	Mindfulness towards thoughts	Situational analysis	Self-exploration with touch
5	Being present during sexual activity	Vertical arrow technique	Self-exploration with touch
6	Letting go	Cognitive restructuring	Sensate focus exercises
7	Detached awareness	Cognitive restructuring	Sensate focus exercises
8	Addressing difficulties	Working with cognitive methods after the intervention	Summary of Modules 1-7

COPE Program (I-CBT)

The focus of COPE are cognitive behavioral techniques that are commonly used in the treatment of mental health problems such as depression and anxiety. In Module 3, participants will learn about automatic thoughts and cognitive distortions [41] and will receive information about the relationship between cognitions, emotions, and behavior. Participants will be asked to identify their automatic thoughts about sexuality, sexual desire, and sexual relationships and will be encouraged to pinpoint underlying thought distortions. In Modules 3 and 4, participants will learn about situational analysis [42,43], and will be guided to apply this method to a personal situation relevant to their low desire (eg, declining a partner's sexual initiative). Situational analysis can be used to improve understanding of the bidirectional relationship between inner experiences (ie, thoughts and feelings) and overt behavior (ie, what someone does or says) in interpersonal situations. It can be a means to identify problematic thought and behavior patterns and encourages individuals to think about strategies for more positive outcomes in future situations. In Module 5, participants will be introduced to the concept of maladaptive cognitive schemas. They will learn about underlying processes and the way in which schemas develop over the lifespan. They will be asked to identify their own negative concepts related to low sexual desire using the downward arrow technique [41]. Building on content of previous modules, challenging schemas and developing alternative thoughts will part of Modules 6 and 7.

MIND Program (I-MBT)

MIND focusses on mindfulness as a therapeutic concept and covers several formal and informal mindfulness-based exercises (eg, body scan, sitting meditation, or mindful eating) adapted from established mindfulness treatments for chronic depression, stress [44], and sexual dysfunctions [45]. Every module starts with a short mindfulness exercises, a so-called Check-In, that invites participants to mindfully focus on different targets such as the breath, negative thoughts, or bodily sensations. In Module 1, participants will learn about the concept of mindfulness in general and will learn about formal mindfulness exercises. In Module 2, they will be introduced to informal mindfulness exercises and breathing meditation. In Module 3, participants will learn detachment from negative thoughts and bodily sensations, as well as acceptance of negative thoughts and emotions. With the progressing mindfulness practice, participants will be encouraged to focus on detachment from all bodily, cognitive, and emotional experiences (Modules 4-6). In Modules 7 and 8, participants will be enabled to consolidate the newly acquired skills into an everyday mindfulness practice.

Treatment Platform

The technology platform used to deliver the interventions is provided by Minddistrict. This company is responsible for the provision and maintenance of the platform. Its content management system is used to upload the interventions, add new participants, and eCoaches. Access to the platform is provided by a combination of email and personalized password. The platform conforms to all required quality standards and operates according to the ISO 27000 and NEN 7510 norms. All data are securely stored on ISO 27000-certified servers and transmitted using HTTPS with SSL certificates (AES-256 and SHA-1, 2048-bit RSA).

Module Format

Each module is built as a series of webpages with each page featuring text-based information, illustrations, audio, or video clips. Three case vignettes are revisited throughout the interventions to provide examples of how different women may benefit from particular aspects of the treatments and how difficulties with certain exercises can be overcome. Additional content (eg, summary of scientific findings) can be accessed by participants who are interested to learn more about a certain topic. Each module is introduced by a summary of the previous content and an overview of the content to follow. A list of all at-home exercises and a short overview of the completed module are provided at the end of all modules. All worksheets and audio files included in the interventions can be accessed over the platform itself. In addition, participants can access study materials via a link to an external online hosting service.

Coaching

eCoaches are female graduate psychology students, specifically trained for the study and supervised by the study coordinator (MM). eCoaches are informed as soon as a participant that is allocated to their account has completed a module. Within the next 48 hours, they provide an individual feedback based on the participants' answers. To increase comparability between eCoaches, they follow guidelines previously outlined for the coaching process. These guidelines were developed based on the existing literature [46,47] and aim to enable eCoaches to establish a therapeutic alliance and a productive therapeutic working environment. Feedback should include empathetic reassurance, unconditional positive regard, guidance on exercises, and encouragement of openness to new experiences. All eCoaches will be supervised by the study coordinator (MM), a clinical psychologist.

Measures

Primary Outcome

The primary outcome is sexual desire, as measured by the Sexual Interest and Desire Inventory-Female (SIDI-F) [48]. The SIDI-F is a 13-item assessment tool validated for use with clinical populations. The item domains assess frequency and intensity of sexual desire and arousal over the past month [49]. An adapted self-report version, called SIDI-F-SR, will be used to assess sexual desire at all assessment points. This self-report scale has been used in studies with women with distressing low sexual desire [17,50] and was found to have good internal consistency. The SIDI-F-SR has shown high agreement with the SIDI-F (ICC 0.86) in a subsample (n=170) of this study. When corrections for the restriction of range were applied, internal consistency of the SIDI-F-SR was 0.91. Test–retest reliability over a period of 14 weeks was good (r=0.74) [51].

Secondary Outcome

The Female Sexual Distress Scale Revised (FSDS-R) [52] is a validated 13-item measure used extensively in treatment outcome studies [53], with 1 item specifically assessing sex-related distress due to low sexual desire. The FSDS-R covers the frequency of negative cognitions or emotions women experience with regard to their sexual life overall, sexual problems, or sexual relationships. Items are rated on a 5-point Likert-scale (never to always), resulting in a total score ranging from 0-52. Higher scores indicate higher levels of distress. In previous studies, the FSDS-R has displayed good discriminant validity, high test–retest reliability, and high internal consistency [52].

Other Measures

Other measures will comprise sociodemographic variables (eg, age, education, relationship status, and duration), symptom checklists, and a standardized clinical interview for diagnoses according to DSM-5 [54,55]. For an overview of measures, see Table 2. Relationship satisfaction will be assessed with the Relationship Assessment Scale [56]. Sexual communication will be assessed with the Dyadic Sexual Communication Scale [57,58] and mindfulness, body image, and body connection will be assessed by the Mindful Attention and Awareness Scale [59], Body Image Self-Consciousness Scale [60], and the Scale of Body Connection [61], respectively. Possible adverse effects of the interventions will be assessed with the Inventory for the Assessment of Negative Effects of Psychotherapy [62]. Experiences with traumatic events or childhood abuse will be assessed with a subsection of the Childhood Trauma Questionnaire [63-65]. Levels of depression and general anxiety will be measured by the Patient Health Questionnaire 9 [66] and the Generalized Anxiety Disorder 7 [67], respectively. Sexual excitation and sexual inhibition will be assessed with a short version of the Sexual Inhibition/Sexual Excitation Scales [68,69]. Compassionate attitude toward one self will be measured by the Self-Compassion Scale [70]. The level of involvement with thoughts about sexuality will be assessed by the Rumination subscale of the Rumination-Reflection Questionnaire [71,72]. Reasons for drop-out, help-seeking behavior, and reasons for nonutilization of health care for sexual problems will be measured with self-developed items. The relationship between eCoach and participant will be measured with the Helping Alliance Questionnaire [73], whereas overall satisfaction with the program will be measured with an adapted version of the Client Satisfaction Questionnaire [74].

Table 2. Overview of measures.

Measure	Timepoint					
	T0	T1	T2	T3	T4	T5
Sexual Interest and Desire Inventory-Female (self-report version: SIDI-F-SR)	—[a]	X	X	X	X	X
Female Sexual Distress Scale Revised	—	X	X	X	X	X
Other measures (in alphabetical order)						
Body Image Self-Consciousness Scale	—	X	—	X	X	X
Childhood Trauma Questionnaire (Subscales for Sexual, Physical, and Emotional Abuse)	X	X	—	—	—	—
Client Satisfaction Questionnaire adapted to internet-based interventions (CSQ-I)	—	—	X	X	—	X
Diagnosis checklist for sexual dysfunctions (ICD-10[b] and DSM-5[c])	X	—	—	—	—	—
Dyadic Sexual Communication Scale	—	X	—	X	X	X
Generalized Anxiety Disorder 7	—	X	—	X	X	X
Inventory for the Assessment of Negative Effects of Psychotherapy	—	—	—	X	X	X
Mindful Attention and Awareness Scale	—	X	—	X	X	X
Patient Health Questionnaire 9	—	X	—	X	X	X
Potential reasons for dropout	—	—	—	X	X	X
Relationship Assessment Scale	—	X	—	X	X	X
Rumination-Reflection Questionnaire	—	X	—	X	X	X
Scale of Body Connection	—	X	—	X	X	X
Self-Compassion Scale	—	X	—	X	X	X
Sexual Inhibition/Sexual Excitation Scales (short version)	—	X	—	X	X	X
Sociodemographic questionnaire	X	X	—	X	X	X
Utilization of additional help	—	—	—	X	X	X

[a]Dashes indicate that the measure will not be assessed.

[b]ICD-10: tenth edition of the International Classification of Diseases.

[c]DSM: fifth edition of the Diagnostic and Statistical Manual of Mental Disorders.

Qualitative Interviews

To gain insights into idiosyncratic factors influencing adherence and acceptance of COPE and MIND, structured telephone interviews will be conducted. Twelve weeks after randomization, participants in active conditions who have accessed at least four modules will be invited to take part in the interview until 25 interviews per active condition are completed. The interview questions cover topics such as experiences with the program, perceived changes and improvements, and their view on helpfulness of the coaching (see Multimedia Appendix 1 for a list of interview questions). Interviews will be conducted by trained graduate psychology students not involved in the eCoaching of the respective participant or the study coordinator (MM).

Experimental Tasks

To assess the impact of the interventions on sexuality-related interpretations and associations, participants will be asked to complete 2 reaction-time paradigms at T1 and T3. To complete these paradigms, they will be asked to download a small computer program (ie, Inquisit 5 Web App) to their computer. Instructions on how to install the program will be provided in an email and on the download website. Sexuality-related associations will be assessed with a STIAT, an experimental task prompting participants to categorize stimuli into different categories as quickly as possible [75,76]. Reaction times are used as a behavioral reference toward the presented stimuli material. The underlying assumption of the task is that strongly associated stimuli are processed more quickly compared to weakly associated stimuli, as reflected in participants' categorization speed (eg, faster reaction times when sexual pictures are paired with the category "I don't want" as compared to "I want"). Sexuality-related interpretations will be assessed with an SST that requires participants to sort 6 words presented on a computer screen (eg, “desire I sexual often feel seldom”) into a grammatically correct sentence, using only 5 words [77,78]. Depending on the omitted word, the resulting sentence can have a positive (eg, “I often feel sexual desire”) or negative valence (eg, “I seldom feel sexual desire”). A study using a convenience sample of women with mixed levels of sexual desire suggested that lower levels of desire are associated with more negative sentences in the SST [79].

Statistical Analyses

Analyses will be conducted and reported according to the CONSORT guidelines [30]. An intention-to-treat approach will be employed to analyze data. Missing data will be handled using

multiple imputations [80]. In addition, study completer analyses including only participants who completed data assessments and intervention completer analyses including only participants who completed all treatment modules will be conducted. Differences in the primary and secondary outcomes between each of the active conditions (ie, I-CBT and I-MBT) and the waitlist control group will be examined with repeated measures ANOVA, and standardized effect sizes (Cohen *d*) and their respective confidence intervals will be calculated for comparison. Predictors and moderators of change will be analyzed via structural equation modeling on an exploratory basis. For statistical analyses, the significance level will be set at $P<.05$, 2-sided, or $P<.025$, 2-sided, in cases where 2 parallel analyses for each of the active conditions are conducted.

Results

Recruitment has begun in January 2019 and is expected to be completed in August 2021. Results will be published in 2022. We anticipate improvements in our primary (ie, sexual desire as measured with the SIDI-F-SR) and secondary outcomes (ie, sexual distress as measured with the FSDS-R) from pretreatment to posttreatment in the I-CBT and I-MBT conditions compared to the waitlist. These improvements are expected to be sustained at 6- and 12-month follow-up. No significant difference in outcomes between active conditions is expected. However, potential differences in efficacy between active conditions will be explored, and the trial will be sufficiently powered to identify medium to large differences between I-CBT and I-MBT.

Discussion

Protocol Overview

Low sexual desire negatively affects millions of women and their partners. Psychological interventions are effective to improve sexual desire and sexual satisfaction [15] but only a minority of women have access to qualified care providers (ie, sexual therapists). Evaluating the efficacy of psychological internet-based interventions is key to solve this problem and to provide help for women in need. Both cognitive behavioral and mindfulness-based treatments are commonly used to treat sexual dysfunctions [15]. To assess whether these therapeutic approaches are feasible and effective when delivered via the internet and to explore for which groups of patients one or both of the treatments are most beneficial are the goals of this trial.

Strategies for Mitigating Challenges

With regard to potential challenges, nonadherence to treatment and attrition are common problems that affect studies of psychological treatments in general, and of internet-based interventions in particular. To address this issue, we will include extensive adherence reminders via email and telephone as well as guidance by eCoaches, which has been linked to higher treatment adherence in internet-based interventions [81]. eCoaches are instructed to closely monitor potential adverse effects (eg, deterioration of symptoms) in participants. If a woman experiences any adverse effects, eCoaches may offer guidance and help in the form of additional text messages via the treatment platform. In more serious cases (ie, a participant experiencing severe distress), the study coordinator (MM) may contact the participant via phone to provide further support. In Module 8, participants can also access information on further treatment options (eg, face-to-face therapy). Moreover, we will assess potential side effects of the treatment with the Inventory for the Assessment of Negative Effects of Psychotherapy at T3 and T4 [62]. In order to ensure high quality care and to provide help in difficult situations (eg, in dealing with dissatisfied participants), eCoaches will receive continuous support by the study coordinator (MM).

Study Contribution

This study will close an important gap in the literature and will show whether cognitive behavioral and mindfulness-based internet interventions are effective in improving low desire in women with HSDD. While uncontrolled and small-scale studies point in this direction, this study will add to the literature by employing a larger sample of women and including longer follow-up intervals. Thus, our study will provide first evidence of whether treatment effects can be sustained over several months. If the results for I-CBT and/or I-MBT are promising, this study should contribute to an improvement of the care situation for women with low sexual desire. Comprehensive data assessments pretreatment, peritreatment, and posttreatment will allow us to investigate moderators and mediators of change and provide important information on *how* I-CBT and I-MBT are working.

Limitations

This study is sufficiently powered to allow for a comparison of I-CBT and I-MBT to a waitlist control group for our primary outcome measure (ie, the SIDI-F-SR). Thus, it will not allow us to identify smaller differences in efficacy between the 2 active conditions or subtle changes in other variables. Although efforts have been made to create study content that should be appropriate and helpful for a wide variety of participants (eg, optional content, case vignettes with women of different ages, partnership status, and sexual orientations), not all women may find the interventions suited for their needs. All treatment modules include audiovisual content (eg, infographics, videos, audio files) to supplement text-based information; still, women with reading difficulties or non-German speakers might find study participation difficult. The same problem applies to the data assessments which mostly rely on internet-based self-report questionnaires. Some participants may need up to 50 minutes to complete data assessments which require a high level of commitment and concentration and place an additional burden on participants.

Conclusion

This study will be the first comprehensive RCT to investigate the efficacy of I-CBT and I-MBT for the treatment of HSDD in women. It will provide insights into new applications of evidence-based treatments, helping to disseminate new options to women, who would not have sought out other treatments due lack of access to sexual therapists or fear of stigmatization. The study findings may also shed light on potential mechanisms of change and help to improve clinical decision making for women with HSDD.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Follow-up interview.
[DOCX File , 41 KB - resprot_v9i9e20326_app1.docx]

Multimedia Appendix 2
Peer review report.
[PDF File (Adobe PDF File), 576 KB - resprot_v9i9e20326_app2.pdf]

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Abbreviations

CBT: cognitive behavioral therapy
CONSORT: Consolidated Standards of Reporting Trials
DSM: fifth edition of the Diagnostic and Statistical Manual of Mental Disorders
FSDS-R: Female Sexual Distress Scale Revised
HSDD: hypoactive sexual desire dysfunction (formerly hypoactive sexual desire disorder)
I-CBT: internet-based CBT
ICD-10: tenth edition of the International Classification of Diseases
I-MBT: internet-based MBT

MBT: mindfulness-based therapy
RCT: randomized controlled trial
SIDI-F: Sexual Interest and Desire Inventory-Female
SST: Scrambled Sentences Task
STIAT: Single-Target Implicit Association Test

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Protocol

Prospective Comparison of 18F-Choline Positron Emission Tomography/Computed Tomography (PET/CT) and 18F-Fluorodeoxyglucose (FDG) PET/CT in the Initial Workup of Multiple Myeloma: Study Protocol of a Prospective Imaging Trial

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Abstract

Background: The International Myeloma Working Group recommends the use of 18-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) for treatment response evaluation, as it is superior to magnetic resonance imaging (MRI). However, at initial staging, the sensitivity of FDG-PET remains inferior to that of MRI. Therefore, there is a need for an imaging technique that could have a sensitivity equal to that of MRI at diagnosis and could serve to evaluate therapy. 18F-choline has shown increased sensitivity when compared with 18-FDG, with about 75% more lesions detected in patients with relapsed or progressive multiple myeloma (MM).

Objective: Our primary objective is to prospectively compare the detection rate of bone lesions by 18F-choline PET/CT (FCH-PET) and FDG-PET in newly diagnosed MM. Our secondary objectives are to assess the accuracy of both PET modalities for the detection of bone lesions and the diagnosis of diffuse disease, to assess the detection rate of extramedullary lesions.

Methods: We will prospectively include 30 patients in a paired comparative accuracy study. Patients with de novo MM will undergo FCH-PET, FDG-PET, and whole-body MRI (WB-MRI) within a 3-week period. WB-MRI will be composed of conventional sequences on the spine and pelvis and of whole-body diffusion axial sequences. The following 6 skeletal areas will be defined: skull, sternum/costal grid, spine, pelvis, superior limbs, and inferior limbs. The number of focal lesions, their respective localization, and intensity of uptake will be retrieved for each skeletal area. Readings will be performed blinded from other imaging techniques. The reference standard will be WB-MRI. Focal lesions present on PET/CT but not on WB-MRI will require a decision made with a consensus of experts based on clinical and imaging data. The number of bone lesions and number of extramedullary lesions will be compared using the Wilcoxon test. The accuracy of FCH-PET and FDG-PET will be compared using the McNemar test.

Results: The study started in September 2019, and enrollment is ongoing. As of June 2020, 8 participants have been included. Data collection is expected to be completed in June 2021, and the results are expected to be available in December 2021.

Conclusions: This study will assess if FCH-PET is superior to FDG-PET for the evaluation of MM tumor burden. This will pave the way for future prospective evaluations of the prognostic value of 18-FCH for treatment response evaluation in MM patients. Additionally, this work may provide new perspectives for better assessment of the risk of smoldering MM progressing to MM.

Trial Registration: ClinicalTrials.gov NCT03891914; https://clinicaltrials.gov/ct2/show/NCT03891914
International Registered Report Identifier (IRRID): DERR1-10.2196/17850

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KEYWORDS

multiple myeloma; PET/CT; MRI; 18-FDG; 18F-choline; cancer; medical imaging; skeletal system

Introduction

Multiple myeloma (MM) is the second most frequently occurring hematological malignancy, with an incidence rate in Europe of 7.4/100,000 men per year and 3.8/100,000 women per year [1,2]. The median age at diagnosis is 69 years [2,3].

MM is defined by the clonal proliferation of more than 10% of malignant plasma cells in the bone marrow associated with signs of myeloma-related organ dysfunction including anemia, hypercalcemia, bone lesions, and renal impairment.

During the past decade, the median overall survival period has almost doubled, from a median of 3 years to 6 years, mainly due to the expansion of the therapeutic arsenal with the use of proteasome inhibitors and immunomodulatory drugs [4]. While the proportion of patients reaching a complete response has increased, the majority of patients eventually relapse. The survival of patients with MM mainly depends on prognostic factors at initial workup. These factors include age, performance status, extramedullary disease, the revised International Staging System stage, cytogenetic abnormalities, and tumor burden [5]. Another important prognostic factor is the depth of the biological response to treatment. This is currently assessed by measuring the level of secreted monoclonal protein in the blood or urine. Complementarily, evaluation of minimal residual disease (MRD) is increasingly performed to finely evaluate patient's treatment response with the use of multiparameter flow cytometry or next-generation sequencing [6]. However, MRD assessment requires a sample of bone marrow, usually taken from the iliac crests. MRD diagnostic performance can therefore be hampered by the location of residual disease.

Functional imaging such as 18- fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) or magnetic resonance imaging (MRI) can help assess the tumor burden at diagnosis as well as residual disease. Previous studies have shown that 18-FDG PET/CT is superior to MRI for the evaluation of treatment response [7-12]. However, its diagnostic value at initial workup can be challenging for different reasons. First, FDG uptake by myeloma cells can be low because of variations in the glucose metabolism pathway [13]. Second, the depiction of skull lesions is generally hampered because of the high physiological FDG uptake of the brain [14]. Third, 18-FDG PET/CT can miss diffuse infiltration [12,15,16]. Therefore, whole-body MRI (WB-MRI) remains more sensitive than 18-FDG PET/CT for the initial diagnosis of MM [13].

Therefore, finding a radiotracer that could have superior diagnostic value at initial workup would allow for better discrimination of the initial tumor burden and hopefully also be useful to better evaluate the treatment response. Recent years have seen the advent of novel metabolic tracers such as 11C-methionine and 11C-labelled or 18F-labelled choline [17-19].

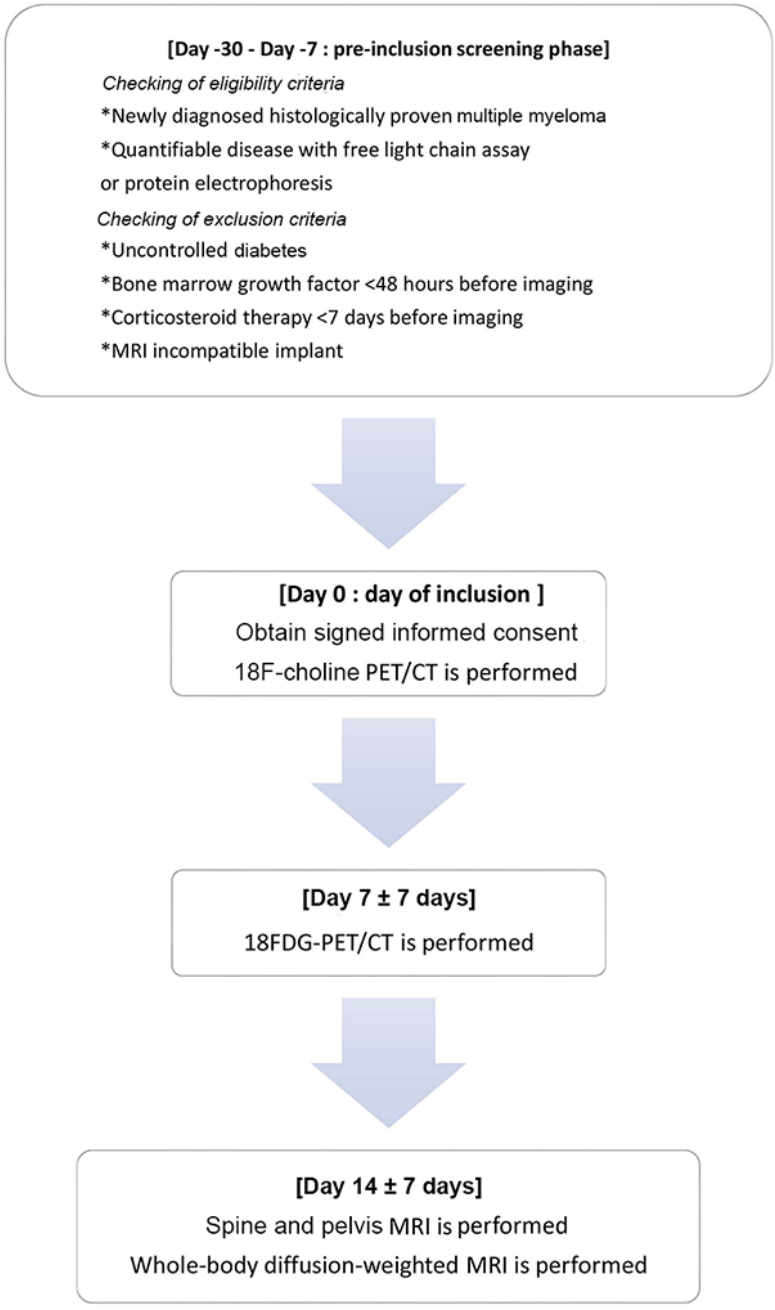
18F-choline, a tracer of phospholipids in the cell membrane, has good availability, as it is used for prostate cancer imaging. In a recent study, 18F-choline showed potential as compared to 18-FDG in MM, with about 75% more lesions detected in patients with MM with suspected relapsing disease [18]. 18F-choline has no physiological uptake in the brain, allowing optimal evaluation of the skull. Also, in this study, the median uptake of 18F-choline was superior to that of 18-FDG [18]. However, the retrospective design and heterogeneous population of this study warrant confirmation from prospective studies. Furthermore, as no reference standard was defined, the diagnostic performance of each modality could not be derived and compared.

Therefore, the current prospective diagnostic accuracy study was designed to compare, in patients with de novo MM, the number of bone lesions detected by 18-FDG PET/CT and 18F-choline PET/CT, with confirmation by a reference standard, in the entire body as well as in predefined skeletal areas (skull, spine, pelvis, ribs-sternum, superior limbs, inferior limbs).

Methods

The scheme of the current prospective trial is shown in Figure 1, and the trial is described hereafter. Within a 21-day period, patients undergo 3 imaging procedures in the following order: 18F-choline PET/CT, 18-FDG PET/CT, and WB-MRI. The second and third imaging procedures will be performed 7 days ± 7 days from the previous procedure.

Figure 1. Flowchart of the current prospective diagnostic trial. CT: computed tomography; FDG: fluorodeoxyglucose; MRI: magnetic resonance imaging; PET: positron emission tomography.



Patient Selection

Inclusion Criteria

Patients with a de novo diagnosis of MM as defined by the International Myeloma Working Group [20] will be prospectively and consecutively recruited at the University Hospital of Bordeaux. Patients must have quantifiable disease, either by the monoclonal component in blood or urine or by free light chain assay. Patients must be older than 18 years and be affiliated with the French social security regimen (or other health insurance regimen). Women of childbearing age must provide a negative pregnancy test before undergoing PET/CTs. Finally, protocol approval signed by the patient and the principal investigator must be obtained by the principal investigator before inclusion.

Exclusion Criteria

Subjects will be excluded if they had any other cancer history in the previous 5 years or if they already had received myeloma treatment. To obtain optimal imaging assessments, we will exclude patients with uncontrolled diabetes, patients that had received injections of bone marrow stimulating growth factor <72 hours before proceeding to PET/CT or MRI, and patients that had received corticosteroids during the 7 days preceding PET/CT. Also, patients with MRI-incompatible implants will be excluded.

18F-Choline PET/CT

Imaging Protocol

Patient must fast for 6 hours before the procedure. 18F-choline is injected with an activity of 3 MBq/kg. Whole-body PET/CT acquisition (from vertex of the skull to the knee) is performed 10 minutes after injection.

Interpretation Criteria

After anonymization, images will be independently read by two experienced nuclear medicine physicians, blinded from clinical data, biological data, and other imaging data performed during the protocol.

18F-choline has physiological uptake by the liver, spleen, pancreas, salivary glands, and urinary tract. Lymph node uptake will not necessarily be considered pathological, particularly in the mediastinum, as lymphadenitis and granulomatosis are sources of false positive findings. Any focal bone uptake will be considered pathological if the uptake is superior to that of surrounding background activity. The following 6 skeletal areas will be defined: skull, sternum-ribs, spine, pelvis, superior limbs, and inferior limbs. The number of focal lesions (FL), localization, and intensity of uptake (SUVmax) will be described for each skeletal area. Diffuse infiltration of the spine will be defined as diffuse spine uptake that is superior to liver uptake [11,14].

18-FDG PET/CT

Imaging Protocol

Patients must fast for 6 hours before proceeding to imaging. 18-FDG is injected with an average dose of 3 MBq/kg. PET/CT is performed from the vertex to the knees 60 minutes after injection.

Interpretation Criteria

After anonymization, images will be independently read by two experienced nuclear medicine physicians, blinded from clinical data, biological data, and other imaging data performed during the protocol.

18-FDG has physiological uptake by the brain, myocardium, kidneys, urinary tract, liver, and spleen. A focal bone lesion is defined as a focal uptake that is superior to surrounding background uptake. An extramedullary lesion will be considered if there is focal uptake within organ or lymph node structures. Of note, bilateral mediastinal lymph node uptake will not be considered as disease, as this will more likely correspond to granulomatosis lesions like sarcoidosis. The same 6 skeletal areas will also be used to classify focal bone lesions. The number of FL, localization, and SUVmax will be retrieved for each skeletal area. Diffuse infiltration will be defined as diffuse spine uptake that is superior to liver uptake [11,14].

Whole-Body MRI (WB-MRI)

Imaging Protocol

WB-MRI examinations will be performed on a 1.5 Tesla device (Aera, Siemens Healthineers, Erlangen, Germany). First, the following imaging protocol will be applied: coronal T1-weighted turbo spin echo sequences on the pelvis (repetition time [TR] 785 ms; echo time [TE] 10 ms), coronal T2-weighted short-term inversion recovery (STIR) sequences on the pelvis (TR 13850 ms; TE 90 ms), sagittal T1-weighted turbo spin echo sequences on the spine (TR 453 ms; TE 12 ms), and sagittal T2-weighted STIR sequences (TR 7450 ms; TE 62 ms). Second, axial diffusion-weighted (DW) sequences will be acquired from the vertex to knees in 7 to 9 stacks. We will apply *b* values of 50 s/mm^2 and 800 s/mm^2. Each stack will be composed of 50 slices of 5-mm thickness (TR 7959 ms; TE 61 ms; inversion time 180 ms). Fused whole-body 3D maximal intensity projection of DW images will be built for analysis. The total length of the MRI protocol will be 45 minutes.

Interpretation Criteria

After anonymization, MRI images will be reviewed by two experienced radiologists blinded from PET/CT, clinical, and biological data. An FL is defined on coronal and sagittal sequences as a lesion with a diameter of more than 5 mm, with a low signal intensity on T1-weighted imaging and a high signal intensity on T2-weighted imaging. On DW images, an FL is defined as focal intensity above the bone marrow background signal. Diffuse bone marrow infiltration is defined based on previously published criteria [21]: a vertebral body to vertebral disk signal ratio <1.3 on T1-weighted images, vertebral body to psoas muscle signal ratio >2 on T2-weighted images, and vertebral body to kidney signal ratio >1 on DW images. A mild infiltration is defined as a pathological finding on T2-weighted or DW sequences. A moderate infiltration is defined as a pathological finding on both T2-weighted and DW images; a severe infiltration is defined as a pathological finding on both aforementioned sequences and on T1-weighted images.

Reference Standard

The reference standard is WB-MRI, which is comprised of conventional MRI sequences combined with WB-MRI diffusion acquisition. Each FL found on 18F-choline or 18-FDG PET/CT and not present on MRI will undergo multidisciplinary consensus between hematologists, nuclear medicine physicians, and radiology physicians. A decision will be reached and will classify an FL as a true-positive or false-positive finding based on patient charts and results from 18-FDG PET/CT, 18F-choline PET/CT, and WB-MRI at baseline but also based on lesion response to chemotherapy during a 12-month follow-up.

Primary Outcome Measures

Number of Whole-Body Bone Lesions on 18F-Choline PET/CT and 18-FDG PET/CT

Every bone lesion will be validated using the reference standard, which is WB-MRI. A bone lesion that is not present on MRI but is present on any of the PET modalities must be validated by an expert multidisciplinary consensus.

Number of Bone Lesions Within Defined Skeletal Areas on 18F-Choline PET/CT and 18-FDG PET/CT

The following 6 skeletal areas will be defined: skull, spine, pelvis, sternum and ribs, superior limbs, inferior limbs. The number of bone lesions in each of these skeletal areas is assessed. Each bone lesion must be validated as mentioned in the previous paragraph.

Secondary Outcome Measures

Diagnostic Accuracy of 18F-Choline PET/CT and 18-FDG PET/CT for the Detection of Focal Bone Lesions

Sensitivity, specificity, positive and negative predictive values, and diagnostic likelihood ratios of each test will be calculated based on two different reference tests. The first reference test will be standard MRI sequences (T1-weighted turbo spin echo sequences, T2-STIR). The second reference test will be a reference standard composed of standard MRI sequences plus DW WB-MRI acquisitions.

Diagnostic Accuracy of 18F-Choline PET/CT and 18-FDG PET/CT for the Detection of Diffuse Infiltration of the Spine

Sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic likelihood ratios of each test will be calculated based on WB-MRI results.

Number of Extramedullary Lesions on 18F-Choline PET/CT and 18-FDG PET/CT

The number of extramedullary lesions detected by each test will be compared.

Sample Size Calculation and Statistics

The main objective is to compare the number of FL detected on 18F-choline PET/CT and 18-FDG PET/CT, after confirming that each lesion exists on the reference standard. Data from a recent article showed that 18F-choline detects 75% more bone lesions than 18-FDG PET/CT [22]. Intrapatient concordance was 0.85. For each tracer, the standard error and mean of the distribution of the number of lesions wsere equal. We hypothesized that we will observe an average number of 10 bone lesions on 18-FDG PET/CT and that this number will increase by 75% on 18F-choline.

With a type I error of 5% and power of 90%, it will be necessary to include 23 patients. Due to the probability that the number of lesions will not follow a normal distribution, we will use a Wilcoxon signed-rank test, which is less powerful than the Student *t* test. To compensate for this lack of power, we will include 30 patients.

The secondary objectives are to compare the global accuracy of 18F-choline PET/CT and 18-FDG PET/CT as well as the accuracy of these two modalities in each of the 6 skeletal areas defined earlier for the detection of MM bone lesions. Accuracies of each modality will be compared using the McNemar test. Other secondary objectives will include the comparison of the accuracies of 18F-choline PET/CT and 18-FDG PET/CT for detecting diffuse infiltration of the spine using the McNemar test. Comparison of the number of extramedullary lesions detected by 18-FDG PET/CT and 18F-choline PET/CT will be performed using the Wilcoxon signed-rank test.

Interobserver and intraobserver agreements of PET/CT readings will be evaluated using the Cohen kappa coefficient.

Research Monitoring

Scientific Research Council

The Scientific Research Council meets according to the needs of the study and at least once a year. Its mission is to make any important decision at the request of the coordinating investigator regarding the smooth running of research and compliance with the protocol. It enquires about the research progress, possible issues, and available results at the Center for Methodology and Data Management and the research coordinating center of the state. The council makes decisions about any relevant modification of the protocol necessary for the continuation of the research; in particular, the council make decisions about strategies to facilitate recruitment in research, discussion of the results, and the publication strategy of these results. The Scientific Research Council can propose to prolong or interrupt the research if the rate of inclusion is too slow, if there are too many people lost to follow-up, if there are too many major violations of the protocol, or for medical or administrative reasons.

Independent Data Monitoring Committee

The only investigation procedure for this research is 18F-choline PET-CT. 18F-choline has had marketing authorization in France since 2010 and is used in clinical routine for the search for metastases in prostatic adenocarcinoma and for the extension assessment of well-differentiated hepatocellular carcinomas. There are no adverse effects reported to date with this radiotracer. Given these elements, the study does not pose any additional risk for the study participants. In conclusion, an independent monitoring committee is not necessary.

Data Collection and Management

Instructions for Data Collection

All information and data required by the protocol will be recorded in paper notebooks, and an explanation should be provided for each piece of missing data. The data must be collected as soon as they are obtained and clearly and legibly transcribed in these notebooks.

Data Management

Data are double entered. The first entry is made using EpiData (EpiData Association, Odense, Denmark), and validation is performed via a different operator using DBS software (DBS Software and Services, Clearwater, MI). In case of needed

transfer, data will be transferred to the Methodology and Data Management Center via a secure FTP channel.

Software used are ACCESS (SAS Institute Inc, Cary, NC) and SAS (SAS Institute Inc, Cary, NC).

The study data remain stored on the server of the director of information systems of the Bordeaux University Hospital, in accordance with the current regulations. A physical copy is kept by the promoter in accordance with the current regulations.

Deviations to the Protocol

Participants Lost to Follow-Up

A participant is considered lost to follow-up when he or she stops the planned 12-month follow-up under the protocol without a reason known to the investigator, so that data collection cannot proceed as planned. The absence of news for more than 1 month defines lost to follow-up.

Data for participants lost to follow-up will be actively researched by the investigator.

Participants Incorrectly Included

A participant is considered to be wrongly included when he or she was actually included in the search even though he or she did not meet all the eligibility criteria. Participants wrongly included should be discussed with the Scientific Research Council. They must continue to be monitored as per the protocol until a decision is made by the Scientific Research Council.

Management of Adverse Events and Other Unintended Effects

The investigator is responsible for the collection of adverse events that occur between the date of written consent and the end of the participant's participation. The investigator must notify the security and vigilance unit by fax or mail, without delay as of the day when he knows of any serious adverse event. The security and vigilance unit shall immediately declare new facts that have arisen during the search to the French National Agency for the Security of Drugs and Health Products (ANSM) and the Committee for the Protection of Persons (CPP).

Annual Security Report

On the anniversary date of the research authorization, the security and vigilance unit will create a security report comprising the list of serious adverse events likely to be related to the experimental procedures including expected and unexpected serious events that occurred during the trial during the period covered by the report, which will include a concise and critical analysis of the safety of the participants who are suitable for research. This report is sent to the ANSM and the CPP within 60 days of the anniversary date of the authorization of research.

Ethical and Regulatory Considerations

The sponsor and investigator undertake to ensure that this research is conducted in accordance with the law relating to research involving the human person (n° 2012-300 of March 5, 2012) as well as in agreement with Good Clinical Practice (International Conference on Harmonization version 4 dated November 9, 2016 and decision dated November 24, 2006) and the Declaration of Helsinki [23].

This research received the favorable opinion of the CPP Sud Méditerrannée I and the authorization of the ANSM. The University Hospital of Bordeaux, sponsor of this research, has signed a liability insurance contract with Gerling-Biomedicinsure in accordance with the provisions of the Public Health law. The data recorded during this research are the subject of computerized processing at the methodological support unit for clinical and epidemiological research in compliance with law n ° 78-17 (dated January 6, 1978) relating to computers, files, and freedoms amended by law 2004-801 (dated August 6, 2004).

Amendments to the Protocol

Any substantial modification must receive, prior to its implementation, a favorable opinion from the CPP and an authorization from the ANSM. Non-substantial changes (ie, those that have no significant impact on any aspect research) are communicated to the CPP for information purposes. All changes are validated by the sponsor and by all research stakeholders concerned before submission to the CPP and ANSM.

Results

The study started in September 2019, and enrollment is ongoing. As of June 2020, 8 participants have been included. Data collection is expected to be completed in June 2021, and the results are expected to be available December 2021.

Discussion

Overview

A recent study showed that the rate of false-negative results for 18-FDG PET/CT for the detection of bone disease in MM is about 10%, which could be attributed to a lower expression of hexokinase 2 [13]. A more sensitive tracer is therefore needed.

The role of 18F-choline in the management of relapsed prostate cancer is well-established, and it also has a role in the characterization of hepatocellular carcinoma. However, it remains poorly explored in the field of hematological diseases. 18F-choline is incorporated into the membrane of cells in division and could reflect the higher rate of neoplastic plasma cells.

A recent retrospective study has shown that 18F-choline detects 75% more focal bone uptakes than 18-FDG PET/CT [18]. However, this study was performed on a heterogeneous previously treated population with suspected progressive disease or relapse. It is known that 18-FDG metabolism in myeloma cells can change after first-line treatment and that FDG-negative myeloma cases at diagnosis can turn FDG-positive when they relapse [13].

This prospective comparative study of diagnostic accuracies will evaluate if 18F-choline PET/CT is superior to 18-FDG PET/CT in a homogenous population with de novo MM. The expected role (according to STARD 2015 definitions) of

18F-choline PET/CT is the replacement of 18-FDG PET/CT. The study has been designed to comply with QUADAS 2 guidelines. We will carefully exclude patients that are already being treated with corticosteroids because of the increased risk of false-negative findings on 18-FDG PET/CT and patients that had a recent injection of bone marrow stimulation factors because of the risk of a false-positive assessment of bone marrow on PET/CT and MRI [14]. Also, 18-FDG PET/CT, 18F-choline, and WB-MRI will be performed within a short time period to avoid misinterpretation due to the apparition of new bone lesions during the protocol.

By analyzing the number of bone lesions per skeletal area, we expect to find that 18F-choline is superior to 18-FDG PET/CT for the detection of bone lesions, especially in the skull, as 18F-choline has no brain uptake. A previous study showed that the median uptake of 18F-choline is higher than that of 18-FDG [18]. Hence, we expect that 18F-choline PET/CT will be more sensitive than 18-FDG PET/CT for the detection of focal bone lesions as well as for the detection of diffuse infiltration.

Several studies have demonstrated that 18-FDG PET/CT remains the most performant imaging procedure for the assessment of MM response to chemotherapy [7-9,11]. However, treatment response assessment would benefit from a baseline evaluation that would depict all existing lesions. Hence, the current study will pave the way for future prospective studies that will aim at evaluating 18F-choline as a tool to evaluate treatment response in patients with MM, in comparison with 18-FDG PET/CT. Therefore, there is hope that we can find a "one-stop-shop" imaging procedure that would perform equally to MRI at diagnosis and with a prognostic value equal or superior to 18-FDG PET/CT.

Smoldering multiple myeloma (SMM) is defined as clonal plasma cell proliferation with 10-60% of plasma cells in the bone marrow, without organ damage. No treatment is required until it reaches the MM stage. The risk of SMM progressing to MM is ~10% each year during the first 5 years [20]. In patients without MM bone lesions on CT, it has been demonstrated that SMM presenting with hypermetabolic foci within the bone had higher chances of progression to MM than without focal uptake [24]. Hence, 18-FDG PET/CT could help stratify the risk of SMM progression to MM. The present prospective study will provide perspectives for the evaluation of SMM with 18F-choline, as a more sensitive tracer would allow even better characterization of the prognosis of patients with SMM.

Conclusions

This study will assess if 18F-choline PET/CT is superior to 18-FDG PET/CT for the evaluation of MM tumor burden. This will pave the way for future prospective evaluations of the prognostic value of 18F-choline PET/CT to evaluate the treatment response in patients with MM. Additionally, this work may provide new perspectives for better assessment of the risk of SMM progressing to MM.

Acknowledgments

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Authors' Contributions

CM, GM, and EH conceived the idea. All authors participated in the design of this study. CM, GM, EH, and LB drafted the manuscript. VL, JA, and PP provided critical important intellectual contributions to the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

Curium Pharma graciously provided 20 doses of 18F-choline.

Multimedia Appendix 1
External reviewing 1.
[PDF File (Adobe PDF File), 216 KB - resprot_v9i9e17850_app1.pdf]

Multimedia Appendix 2
External reviewing 2.
[PDF File (Adobe PDF File), 213 KB - resprot_v9i9e17850_app2.pdf]

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Abbreviations

ANSM: French National Agency for the Security of Drugs and Health Products
CPP: Committee for the Protection of Persons
CT: computed tomography
DW: diffusion-weighted
FDG: fluorodeoxyglucose
MM: multiple myeloma
MRD: minimal residual disease
MRI: magnetic resonance imaging
PET: positron emission tomography
SMM: smoldering multiple myeloma
STIR: short-term inversion recovery
TE: echo time
TR: repetition time
WB-MRI: whole-body MRI

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Protocol

Effectiveness of Social Cognitive Theory–Based Interventions for Glycemic Control in Adults With Type 2 Diabetes Mellitus: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: For those living with type 2 diabetes mellitus (T2DM), failing to engage in self-management behaviors leads to poor glycemic control. Social cognitive theory (SCT) has been shown to improve health behaviors by altering cognitive processes and increasing an individual's belief in their ability to accomplish a task.

Objective: We aim to present a protocol for a systematic review and meta-analysis to systematically identify, evaluate, and analyze the effect of SCT-based interventions to improve glycemic control in adults with T2DM.

Methods: This protocol follows the 2009 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. Data sources will include PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsychINFO, Cochrane Library, and Web of Science, and data will be reviewed with the use of customized text mining software. Studies examining SCT-based behavioral interventions for adults diagnosed with T2DM in randomized controlled trials located in the outpatient setting will be included. Intervention effectiveness will be compared with routine care. Screening and data collection will be performed in multiple stages with three reviewers as follows: (1) an independent review of titles/abstracts, (2) a full review, and (3) data collection with alternating teams of two reviewers for disputes to be resolved by a third reviewer. Study quality and risk of bias will be assessed by three reviewers using the Cochrane risk of bias tool. Standardized mean differences will be used to describe the intervention effect sizes with regard to self-efficacy and diabetes knowledge. The raw mean difference of HbA1c will be provided in a random effects model and presented in a forest plot. The expected limitations of this study are incomplete data, the need to contact authors, and analysis of various types of glycemic control measures accurately within the same data set.

Results: This protocol was granted institutional review board exemption on October 7, 2019. PROSPERO registration (ID: CRD42020147105) was received on April 28, 2020. The review began on April 29, 2020. The results of the review will be disseminated through conference presentations, peer-reviewed journals, and meetings.

Conclusions: This systematic review will appraise the effectiveness of SCT-based interventions for adults diagnosed with T2DM and provide the most effective interventions for improving health behaviors in these patients.

Trial Registration: PROSPERO CRD42020147105; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=147105

International Registered Report Identifier (IRRID): PRR1-10.2196/17148

(JMIR Res Protoc 2020;9(9):e17148) doi:10.2196/17148

KEYWORDS

social cognitive theory; type 2 diabetes mellitus; glycemic control; self-efficacy; self-management; HbA1c; glycosylated hemoglobin

Introduction

Background

It is estimated that 9.4% of the American population is living with diabetes mellitus, and of these, 90%-95% are diagnosed with type 2 diabetes mellitus (T2DM) [1]. Insulin resistance characterizes T2DM and is often precipitated by lifestyle-associated risk factors [2]. Managing T2DM requires the application of a large amount of knowledge to maintain consistent behaviors. Other requirements for effective diabetes self-management are high levels of discipline and diligence for prudent decision making. Complex medical regimens and poor perception of an ability to control the disease worsen self-management adherence [3,4]. The inadequacy of diabetes self-management and suboptimal glycemic control have been well documented in a national prevalence study involving over 4900 participants. The study examined the prevalence of people who met glycemic targets from 1988 to 2010. Of the 4900 participants, only 2572 (52.5%) experienced glycemic control with a HbA_{1c} value of less than 7% and 2313 (47.2%) of participants had a HbA_{1c} value of over 7% [5,6]. Deficient glycemic control has been attributed to individual pathophysiology progression, poor self-management skills, lack of support, and nonadherence to a healthy lifestyle [5]. The Center for Disease Control and Prevention describes the severe complications of poor glycemic control. Complications include cardiovascular disease, cerebrovascular disease, limb amputation, retinopathy, and renal failure [2].

Theoretical Behavioral Interventions

The use of theory in behavioral research is not new. Theory-based behavioral interventions have been shown to produce longer and lasting glycemic control in adults with T2DM [7,8]. Behavioral interventions direct behavioral change through cognitive pathways [9]. Individualized theoretically based behavioral interventions have been shown to be more effective than a generalized curriculum or routine care alone [8,10,11].

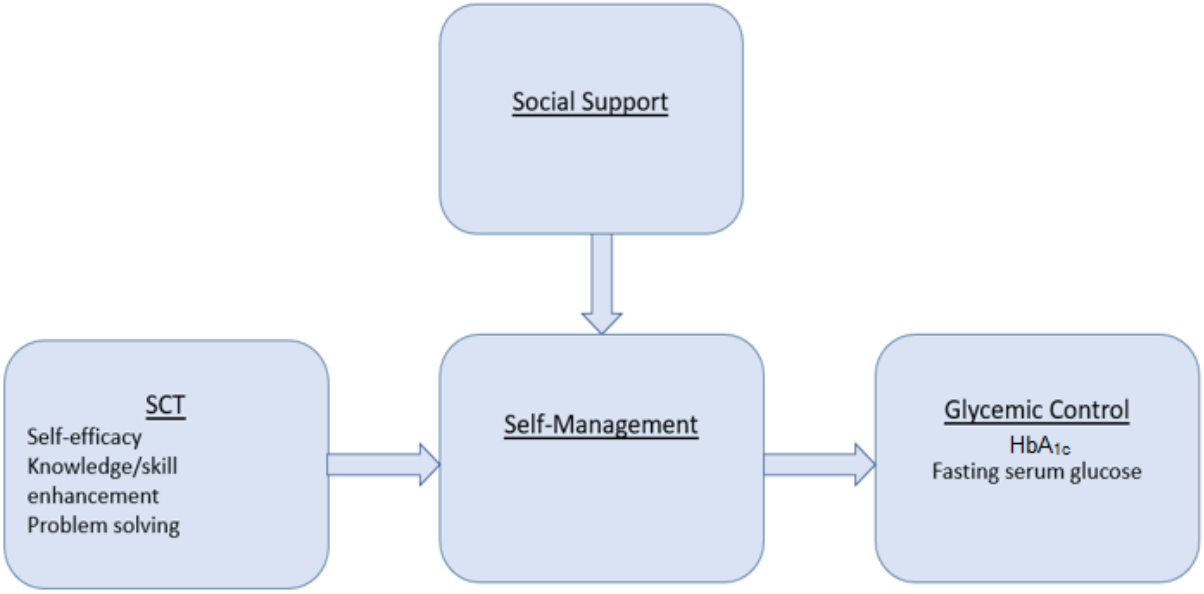
In a scoping literature review examining how current research presents theory-based interventional studies, several goals were considered as follows: (1) which theory or theories were used, (2) which concepts were used as the foundation of an intervention, and (3) what variables were measured compared to the theory and concepts that were identified (Y Smith, MSN, et al., unpublished data, 2019). Among the three criteria, there was one similarity and some inconsistencies that were noted. The one similarity was that one theory consistently held favor among the scientific community and was more commonly used than any other theory. This theory was social cognitive theory (SCT). Despite collective judgment pointing to the effectiveness of SCT, there are variations of its use within the current literature. For example, (1) only a single concept was identified as the focus, (2) some studies identified one concept but measured another instead, (3) findings were inconsistently reported as both effective and ineffective, and (4) numbers one, two, and three combined were seen in some studies. At initial glance, the inconsistencies could lead to a false conclusion that there is no prevailing effective or singularly dominant theory to reduce glycemia. A deeper investigation is warranted of the use and the reported effectiveness of SCT-based trials. Neglecting further inspection would disregard an apparent consensus on SCT within the scientific community. A systematic review and meta-analysis on the most prevalent theory would confirm or deny the current scientific consensus and identify the most effective interventions to reduce glycemia in adults with T2DM.

Social Cognitive Theory

SCT aims to promote self-management behavior (eg, adopting a healthy lifestyle) through self-regulating cognitive processes [12]. Cognitive processes are more than receiving an education or performing a skill; they are defined as managing complex health conditions (eg, T2DM) to obtain a desired response (eg, optimal glycemic control) [13-15]. Self-management behavior is the cornerstone of effective diabetes care. Based on the SCT, cognitive processes promote self-management behavior by improving knowledge, self-efficacy, and problem-solving skills [16].

Emerging from the scoping review is the SCT-based framework (Figure 1), which has guided this research. In this framework, glycemic control is the outcome of self-management behavior. It is defined as a HbA_{1c} value of less than 7%, fasting serum glucose level between 70 and 130 mg/dL, and serum glucose level of 180 mg/dL 2 hours after a meal [16]. Self-management behavior is made up of various complex daily activities required to reach glycemic targets [4,17-20] and defined as self-monitoring serum glucose, healthy eating, regular physical activity, stress management, problem solving, medication adherence, and goal setting [21-23]. First, SCT-based interventions promote self-management behavior by enhancing diabetes self-management knowledge, which is defined as the general knowledge of diabetes self-management [23]. Second, SCT-based interventions improve self-efficacy, which is defined as the belief one has in themselves to perform a behavior [12]. Lastly, SCT-based interventions improve self-management by enhancing problem-solving skills defined as a series of cognitive operations used to figure out what to do when the way to reach a goal is not apparent [17,24,25]. Social support moderates self-management and includes informational support by providing education or advice. Instrumental support can be financial support or physical assistance with self-management actions. Emotional support provides acceptance and approval, whereas affirmational support provides validation of self-management efforts [17,26,27].

Figure 1. Social cognitive theory–based interventions for glycemic control. SCT: social cognitive theory.



Text Mining

A methodological challenge in conducting this systematic review is the presence of an overwhelming amount of information on adults with T2DM. A GALILEO search using SCT and T2DM as search terms revealed well over 100,000 results. Search results from a variety of databases will include full-text studies, abstracts, books, conference materials, and grey literature, which are discussed in the search strategy below.

To better explore the immense amount of textual evidence, this review proposes to extract information by using the method of text mining [28]. Text mining is a technology-based application that uses semantics as a method of discovery [29]. Although text mining is widely adopted in other fields, there are currently no detectable systematic reviews on theory-based interventional research using this innovative technique. Another strength of text mining is semantic annotation that allows relationships, keywords, or topics to be attached to the concept [30]. The rationale for using this innovative method is exploration to (1) accurately manage the massive amount of literature found for prompt screening, (2) compare text-mined results to reviewer results, (3) show the numerical frequency of the identified concepts in the included literature, (4) know the strength and position of a concept thereby gaining insight into possible mechanisms of action, and (5) create a visual word cloud of the results [31]. The use of text mining enhances the discovery of knowledge and will improve the quality of data extraction. By identifying how the concept is involved in the text, assertions can be made, and they ultimately will increase the fidelity and results of this review.

Objectives

The purpose of this review is to examine the effect of SCT-based behavioral interventions to improve glycemic control in adults with T2DM. We initially hypothesize that patients who receive an SCT-based intervention have better glycemic control. We further hypothesize that patients who receive greater social support have better glycemic control.

The research goals are as follows:

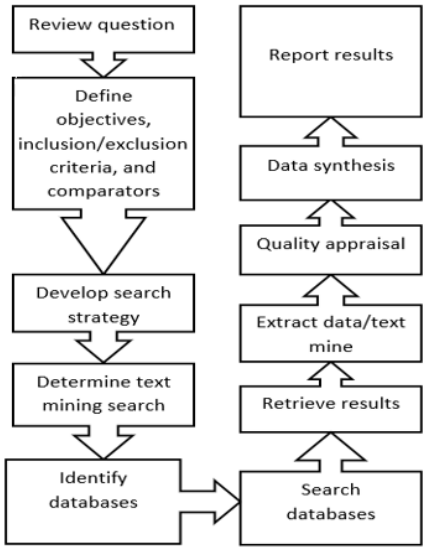
1. To examine the relationships between glycemic control and concepts (ie, self-efficacy, knowledge, and problem-solving) targeted by SCT-based behavioral interventions in adults living with T2DM.
2. To examine the pooled effect of SCT-based interventions on glycemic control (ie, HbA
   1c
   and fasting serum glucose) in adults living with T2DM.
3. To examine the interaction between social support and SCT-based interventions for glycemic control in adults living with T2DM.

Methods

Design

This systematic review follows the 2009 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. The stages of the systematic review are presented in Figure 2.

Figure 2. Stages of the systematic review.



This systematic review will examine randomized controlled trials owing to their inherent strength. Studies with a less rigorous methodology, such as nonrandomized trials, quasiexperimental or observational studies, research protocols, and drug trials, will be excluded. No date restrictions will be applied in searching for eligible studies.

Eligibility

The inclusion criteria are presented in Textbox 1. Studies targeting health care professionals; studies including individuals diagnosed with type 1 diabetes mellitus (T1DM), gestational diabetes, prediabetes, drug-induced diabetes, or metabolic syndrome; and studies including individuals aged less than 18 years will be excluded. Studies set only in the outpatient setting will be included. There will be no restrictions on gender, socioeconomic status, ethnicity, or race.

Textbox 1. Inclusion criteria.

Inclusion criteria
Population: Outpatient setting, previously diagnosed with type 2 diabetes mellitus, and age over 18 years
Intervention: Interventions based on social cognitive theory (SCT) concepts or interventions that use a combination of SCT and another theory, model, or framework, with a minimum 3-month time frame
Comparison: Routine care
Outcomes: HbA_{1c} and fasting serum glucose
Study design: Experimental designs including randomized controlled trials

Outcomes

The primary outcome of interest is glycemic control. Glycemic control will be assessed before and after the intervention. All glycemic control outcomes will be observed and recorded objectively.

Glycemic Control

The HbA_{1c} test is a blood test measuring the average blood glucose level over the past 3 months. Glucose adheres to hemoglobin located within red blood cells. The adherence of glucose to red blood cells is referred to as glycosylated hemoglobin or HbA_{1c} [1]. The secondary measures of glycemic control are fasting blood glucose and postprandial blood glucose.

All studies lasting less than 3 months will be excluded, as HbA_{1c} takes 3 months to manifest. There will be no exclusions regarding the length of follow up. Studies with no comparison, an additional comparison, or an alternative comparison will be excluded, as it is inappropriate to provide anything less than routine care. Included concepts of SCT are self-efficacy, skills, practice, motivation, self-regulation, attitude, expectations, knowledge enhancement/acquisition, skill enhancement/acquisition, social norms, social network, social support, community, experience mastery, efficacy expectation, problem-solving, verbal persuasion, vicarious experience, physiological feedback, reflection, and reward.

Search Strategy

As mentioned above, a GALILEO search using SCT and T2DM search terms presents thousands of results. Completing a GALILEO search begins with the development of key terms; however, this alone can produce results that cover other topics. A comprehensive search strategy has been developed and will be used to complete the literature search in four stages by three reviewers.

Keywords and phrases are derived from the research goals and are the foundation of the search strategy. The search will be completed in four stages. Stage one will involve the development of search terms phrases, descriptions, attributes, or sentences for determining text mining parameters [30]. Examples of key SCT concepts and derived strategies are presented in Table 1. Key concepts and search terms have been gleaned from a previous scoping literature review completed between 2016 and 2018 (Y Smith, MSN, et al., unpublished data, 2019).

Table 1. Social cognitive theory concepts and derived strategies.

Theory	SCT[a] concepts	Derived strategies
SCT	Social learning, social cognitive, feedback, knowledge, attitude, self-efficacy, self-efficacy, confidence, problem-solving, problem solving, coping, coping strategy, vicarious, verbal, motivational, self-regulation, attitudinal, belief, mastery, efficacy expectation, accomplishment, verbal persuasion, vicarious experience, physiological or affective state, physiology feedback, social norms, social network, social support, community, experience mastery, efficacy expectation, and reward	Soap opera, guided group discussion, group cooking, cooking demonstrations, group meals, presentations, messages, self-monitoring demonstrations, cognitive reframing, quizzes, modeling, family support, behavioral "experiments" (or trials), stress management, label reading, review log, reinforcement of positive attitudes, visual aids, goal setting, group "games," support, planning, literacy, color-coded graph, traffic light, log, track, personalized counseling, identifying-strategy, role play or role-play, reflection, group counseling, encouraging, positive feedback, demonstrating, role modeling, assessment, follow-up, follow up, worksheet, and self-help

[a]SCT: social cognitive theory.

Stage two will begin with a broad search of keywords and phrases. An example of a beginning search string is presented in Multimedia Appendix 1. An initial broad search will be used to identify relevant studies and to assist in expanding keywords and phrases for a more in-depth search. A previous search for any systematic reviews on this topic only revealed one study on theory-based educational interventions for adults with T2DM [8]. However, currently, there is no systematic review meta-analysis on SCT-based behavioral interventions for adults with T2DM. To our knowledge, there is no review using text mining in the review process. Existing systematic reviews will be assessed to expand keywords and phrases for a more in-depth search. At minimum, Medline, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and PubMed will be searched during stage two.

Stage three will be an expanded search of key concepts, terms, strategies, and phrases and again will include Medline, CINAHL, and PubMed, along with Web of Science, Ovid, PsycINFO, and Cochrane Library. Additionally, the approach will include ProQuest, a dissertation database, grey literature, a hand search, and a search of the reference lists of included studies. The Boolean operators "AND" and "OR" will be used as connectors for keywords, and mesh terms will be used. Additionally, professional organizations relevant to the review will be searched for reports, guidelines, and unpublished research (eg, the American Diabetes Association).

Stage four will involve a search of the reference lists of identified articles for any relevant references, systematic reviews, and meta-analyses, and a hand search of appropriate journals. Additionally, an author search will be conducted for any publications by Zhao et al [8], as this is currently the only known similar systematic review.

There will be no date restrictions on the searches. Database searches will include peer-reviewed journals, and full-text studies only will be included with reported results. No language restriction will be applied; however, if a study is not translatable, it will be excluded. As the search strategy progresses, a detailed record of search activities will be kept (Multimedia Appendix 2). The timeframe for searching each database will also be maintained; further, if the entire database since inception is not used, a valid reason will be provided. As eligible citations are identified, they will be organized in the EndNote X7 citation manager and then downloaded by the first reviewer into an online publication screening manager (Rayyan) for title and abstract screening.

Publication Selection Criteria

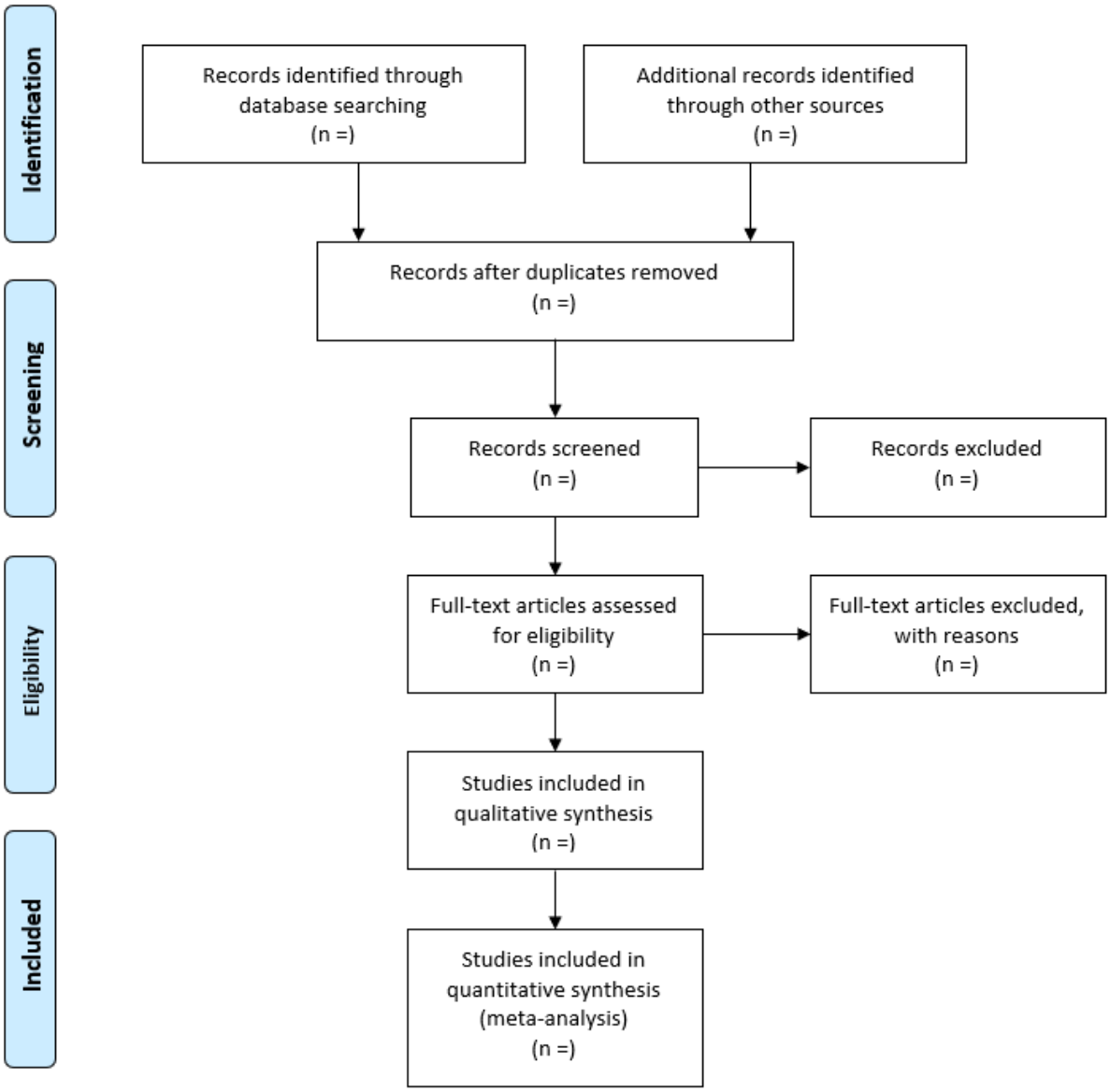
Reviewers will work independently initially and then in teams of two to allow the third reviewer to settle any disputes that may arise. The review team will include a doctoral student as the first reviewer, a doctorally prepared dietician researcher as the second reviewer, a doctorally prepared nursing researcher and a major advisor as the third reviewer, a reference librarian, and a statistician. The first and second reviewers have completed training specializing in systematic reviews and meta-analyses.

A record of search results will be compiled into numbered lists by the first reviewer to create the search log (Multimedia Appendix 2) and will be used to develop the study flow diagram (Figure 3). The search log will document each database search and all rationale for excluding any titles, abstracts, or studies by the first reviewer. Entries for the search log will include the number of included and excluded studies, along with the rationale for exclusion from the independent and full-text review.

The initial screening will be completed by three reviewers on Rayyan, which enables reviewers to screen blindly and independently. The first screening will be of titles and abstracts; duplicates will be removed and noted in the search log. Reviewers will then meet to discuss and take decisions on titles and abstracts that are conflicting in the independent review. Studies that meet the inclusion criteria will be organized in a separate folder in a shared file on Dropbox, and the full-text articles will be retrieved by the first reviewer. Full-text screening will be performed in teams of two reviewers, and data will be collected in the codebook (Multimedia Appendix 3). A hand search will be completed, and included publications will be added for the full-text review.

Text mining will be completed by a project collaborator proficient with customized text mining software. Full-text publications will be preprogrammed and screened by word recognition (Multimedia Appendix 4). Results will be compiled into an excel file (Multimedia Appendix 5). Reviewers will use the text frequency table, systematic annotations, and word cloud to compare results from screening, data extraction, and analysis.

Figure 3. Flow diagram.



Quality Assessment

The review team will follow the 2009 PRISMA checklist to evaluate included studies (Multimedia Appendix 6). Further, the unit of analysis will be assessed to determine at which point randomization occurred to ensure participants are not duplicated in the results. To account for missing data, we will critically evaluate the number of participants before the intervention versus after the intervention, the attrition rates, and if an intention-to-treat analysis was completed. If missing data for calculating effect sizes are present, corresponding authors will be contacted for further information. If two unsuccessful attempts are made to reach a corresponding author within 2 weeks, the article will be excluded. Assessment of the quality of individual studies will be completed by examining the risk of bias and will be conducted while coding. The Cochrane collaboration tool for assessing risk of bias will serve as the guide for assessing bias in the included literature. Judgments for selection, performance, detection, attrition, reporting, and selection bias will be based on answering “yes” or “no” to specific criteria outlined in Multimedia Appendix 7. The two reviewers will assess the risk of bias according to the requirements above and discuss any disputes with the third reviewer.

Data Extraction and Management

The review team will conduct data extraction and management in an Excel spreadsheet. The first reviewer will work closely with the reference librarian to produce an effective search string of all literature. The first and second reviewers and major

advisor understand research design and have the ability to critique research studies. The first and second reviewers will code independently and settle any disputes with the third reviewer. A statistician will ensure that proper analyses are conducted for the different types of data extracted. Extracted data will be coded and defined according to the codebook example in Multimedia Appendix 3. The codebook will be the foundation for a table presenting the characteristics of the included studies. The characteristics of the included studies and their extracted data are reported in an Excel table (Multimedia Appendix 8).

Data Analysis

Standardized mean differences will be used to describe the intervention effect sizes with regard to self-efficacy and diabetes knowledge. To calculate the standardized mean differences, the means, standard deviations, and change scores of the self-efficacy and knowledge evaluation scales will be recorded [13,23-25,32-35].

The standardized mean difference will be considered small (value of 0.2), moderate (value of 0.5), or large (value of 0.8). Individual and overall effect sizes, 95% CIs, variance, and *P* values will be reported. For measures of glycemic control, including HbA_{1c}, finger stick blood sugar, postprandial serum glucose, and random serum glucose, the weighted mean differences will be calculated as the intervention effect sizes. The weighted mean will preferably be calculated with pre-HbA_{1c} levels, change scores, and *P* values, if available. The effect size, variance, and direction of the effect will be evaluated and compared. Individual and overall analyses will be presented in a forest plot and described in the narrative [36].

Heterogeneity will be assessed by visual inspection of the forest plot and chi-square (*Q*) with a significance level of .05, and compared using the I^2 statistic. The *Q* statistic and *P* value offer statistical evidence of heterogeneity. The I^2 details the ratio of between-study variance to total variance and is a display of the magnitude of heterogeneity. The range of I^2 is 0 to 100, and an I^2 value of >50% will be considered to indicate significant heterogeneity. If heterogeneity is indeed present, we will perform a meta-regression to identify where the variation may lie and explain the variation in the narrative. The meta-regression will be performed to explain covariates or characteristics at the study level. A random-effects model will be used [36].

When heterogeneity is present, a subgroup analysis will be conducted to determine if there is a difference between studies that reported SCT exclusively and studies that reported SCT and the use of another theory, model, or framework. The research aims to determine which variation of theory (SCT alone or SCT combined with another theory) is more effective in the analysis. A subgroup analysis will be conducted on those studies reporting a self-efficacy component of the intervention versus a knowledge or skill-enhancing component. Additionally, the research aims to determine if the duration of T2DM has any impact on effect size. Subgroup analysis will be performed by analyzing a pooled or separate T^2 depending on the number of studies in each subgroup and the within-study variance [36]. Additionally, a subgroup analysis will be performed on the moderator of support to determine if any difference exists between the treatment group and the routine care group.

The funnel plot will be examined to assess publication bias by performing a Begg and Mazumdar rank correlation and an Egger regression test. The Begg and Mazumdar test and Egger test determine if the effect size is reflective of the study sample size. The funnel plot will be analyzed to note the presence of symmetry by assessing the distribution of individual effect sizes surrounding the *x*-axis versus the standard error on the *y*-axis. To evaluate whether the overall effect is an object of bias, Orwin fail-safe *N* will be used. Orwin fail-safe *N* allows the determination of how many missing studies are needed to detect an effect greater than zero. Additionally, Orwin fail-safe *N* will be used because it does not require the adjusted effect size to be zero [36].

Additionally, the impact the bias has on the overall effect will be assessed by the Duval and Tweedie trim and fill procedure. The Duval and Tweedie procedure identifies the studies causing an asymmetrical funnel plot. The procedure recalculates the overall effect size of bias to determine how much impact bias has on the overall effect size and if there is a change in the effect when bias is adjusted. Language bias will be assessed by comparing the effect size between English studies and non-English studies, if necessary. The impact of English and non-English studies will be determined by observing the overall effect when English studies are removed from the analysis. Confounding variable bias will be assessed with a subgroup analysis to know whether (1) SCT alone was used versus SCT and another theory, (2) the duration of T2DM changes the effect, or (3) the intervention components impact the overall effect. Judgments regarding the risk of bias (low, moderate, or high) will be made by the reviewing team based on Cochrane criteria for judging the risk of bias [36].

Data analysis will be completed using comprehensive meta-analysis (CMA) [36]. A summary of the findings table will include a random effect meta-analysis to estimate individual and overall effect sizes. A 95% CI and a *P* value will be reported with effect sizes. Further, a summary discussing study limitations, consistency of effects, imprecision, indirectness, and publication bias will be presented. If substantial heterogeneity exists, subgroup analysis and meta-regression for continuous variables will be performed. A subgroup analysis will be performed on the moderator if supported. A tau-squared statistic will be reported, and an explanation of between-study variance will be provided. A sensitivity analysis will be completed to determine the impact of decisions made during the review, if any. Additionally, a sensitivity analysis will be completed to assess the effect of outliers, if any. It is difficult to name specific items that will be analyzed in this protocol owing to attributes that are unidentifiable until the review and analysis are completed.

Data Synthesis

The data will be presented in summary of findings tables and will serve as the foundation for discussing the results. Analysis of the raw mean differences will be provided in a random effects

model and presented in a forest plot. A discussion of the results of each outcome will be presented in narrative form. Further, a discussion of the results of the subgroups and sensitivity analysis will be presented. For each study, the consistency of the pooled effect, precision or imprecision of the effect, and bias will be evaluated and discussed. The results of the study characteristics are presented in Multimedia Appendix 8. A reflection of the methods specified in this proposal will be provided to present any issues that arose in the discussion section. Finally, a discussion in a narrative format on the clinical significance of the results will be provided.

Results

This protocol was granted institutional review board exemption on October 7, 2019, by Augusta University in Augusta, Georgia. PROSPERO registration (ID: CRD42020147105) was received on April 28, 2020. The review began on April 29, 2020. As of May 27, 2020, there are 43 publications included in the review. The results of the study will be disseminated through conference presentations, peer-reviewed journals, and meetings.

Discussion

As with any study, there are expected limitations that will need to be addressed. The limitations include publications reporting incomplete data or analyzing various types of glycemic control measures accurately within the same data set (eg, HbA_{1c} and fasting serum glucose). The authors of studies with missing data will be contacted and given 2 weeks to respond. We will consult with an expert statistician to guide data entry and analysis of the various forms of glycemic measures within the same analysis. Another noted limitation is accurately comparing and interpreting the text-mining results with reviewer results and the CMA results. To our knowledge, there is no other social science study utilizing text mining.

Further, based on our information, this study utilizes the most comprehensive data collection tool of any similar study, with over 90 data points. This protocol is designed based on previous research on the use of various theories to form effective interventions for adults with T2DM. This work will appraise the effectiveness of SCT-based interventions by analyzing the pooled effect of SCT-based interventions on glycemic control. The exploration of reviewer results and text-mining results will produce insights unknown before this study, with the ultimate goal of informing health care providers on the most effective behavioral interventions for improving glycemic control.

Authors' Contributions

The lead author and primary investigator YS developed all aspects of the research in this proposal, with guidance from RG, SC, JL, TM, SS, and LY. RG was involved in study conception and design. SC, JL, TM, and SS were involved in guiding research conception, design, data collection, and data analysis. LY was involved in guiding all aspects of this research. SC, JL, TM, SS, and LY were involved in revising this proposal. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search string example.
[DOCX File , 13 KB - resprot_v9i9e17148_app1.docx]

Multimedia Appendix 2
Search log.
[DOCX File , 14 KB - resprot_v9i9e17148_app2.docx]

Multimedia Appendix 3
Codebook.
[DOCX File , 29 KB - resprot_v9i9e17148_app3.docx]

Multimedia Appendix 4
Social cognitive theory concepts and descriptions.
[DOCX File , 16 KB - resprot_v9i9e17148_app4.docx]

Multimedia Appendix 5
Excel text mining example.
[DOCX File , 13 KB - resprot_v9i9e17148_app5.docx]

Multimedia Appendix 6
PRISMA quality checklist.
[DOCX File , 17 KB - resprot_v9i9e17148_app6.docx]

Multimedia Appendix 7
Cochrane risk of bias tool.
[DOCX File , 15 KB - resprot_v9i9e17148_app7.docx]

Multimedia Appendix 8
Characteristics of the included studies.
[DOCX File , 17 KB - resprot_v9i9e17148_app8.docx]

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Abbreviations

CMA: comprehensive meta-analysis
SCT: social cognitive theory
T1DM: type 1 diabetes mellitus
T2DM: type 2 diabetes mellitus

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Proposal

LEAVES (optimizing the mentaL health and resiliencE of older Adults that haVe lost thEir spouSe via blended, online therapy): Proposal for an Online Service Development and Evaluation

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Abstract

Background: Loss of a spouse is a frequent occurrence in later life. While most older adults successfully process this loss and will return to a normal life, about 10% of the individuals are unable to cope, and progress to prolonged grief (PG). PG, in turn, can result in mental and physical problems including poor sleep, cardiovascular problems, depression, and suicidal tendencies.

Objective: LEAVES (optimizing the mentaL health and resiliencE of older Adults that haVe lost thEir spouSe via blended, online therapy) is an online bereavement program that will support the prevention and treatment of PG, so that elderly mourners can continue to lead an active, meaningful, and dignified life. LEAVES will cater to secondary end users (eg, family, informal caregivers) by reducing stress.

Methods: LEAVES will help older adults to process the loss of a spouse in an online environment, which consists of (1) an existing online grief self-help program LIVIA, (2) the Before You Leave program that allows for storing personal memories, (3) a virtual agent platform, and (4) an accessible front-end design. LEAVES can detect persons at risk for complications, reveal negative trends in their emotional life, and act to counter such trends. The service relies on online support whenever possible but is blended with telephone or face-to-face counseling when necessary.

Results: The project will take place between February 2020 and January 2023 and includes a real-life evaluation in which 315 end users will use the service across 3 countries (the Netherlands, Portugal, and Switzerland). The evaluation of LEAVES will focus on clinical effect, its business case, and technology acceptance. The results will pave the way for smooth integration into existing care paths and reimbursement schemes.

Conclusions: The LEAVES service aims to soften the mourning process, prevents depression or social isolation, strengthens widow(er)s resilience and well-being, and quickens one's return to societal participation.

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KEYWORDS

eHealth; grief; bereavement; widowhood; aged; resilience; telemedicine; mental health

Introduction

Background

> *Mary has been married to Frank for 30 years. Frank is now facing the end of his life, due to progressing cancer. Frank passes away and Mary is left to herself. Mary was always focused on her close family, but now that Frank is gone and her only daughter Lisa has returned to London, she will have to face her mourning process and adaptation to a new life by herself.*

When older adults lose their partner, they often lose the most important person in their life. Most mourners grieve for a period and then find a way to cope with their loss. Some mourners, however, develop severe or persistent grief symptoms, with a clinical diagnosis of a prolonged grief disorder (as defined in International Classification of Diseases [ICD]-11) or a persistent complex bereavement disorder (as defined in Diagnostic and Statistical Manual of Mental Disorders [DSM]-5). Within the context of LEAVES (optimizing the mentaL health and resiliencE of older Adults that haVe lost thEir spouSe via blended, online therapy), we will use the term prolonged grief (PG). PG is the "failure to return to pre-loss levels of performance or states of emotional wellbeing" [1] and commences when grief-related symptoms are still present after 6 months. These symptoms consist of separation distress (eg, yearning, intensive sorrow, and emotional pain), reactive distress (eg, difficulties accepting the loss, self-blame, and avoidance of reminders of the loss), and social/identity disruption (eg, loneliness, meaninglessness, and role confusion), which can lead to impairments in important life domains. Comorbidity of PG with depression, post-traumatic stress disorder, and suicidal ideation is high [2]. Bereavement in later life has also been associated with physical problems and risk behaviors including involuntary weight loss, poor sleep, change in smoking and alcohol habits, chronic pain, inflammation and cardiovascular risks, as well as increased mortality [3-6]. PG has an estimated prevalence of 10% among the general elderly population [7], with the estimated rates differing per gender. For example, a German population-based study found prevalence rates of complicated grief of 9.6% for female and 2.7% for male older adults [8]. A study conducted on a large sample of Dutch older adults found that of those experiencing grief, 25.4% develop PG [9].

The course of the grieving period and whether or not a person develops PG depend on several factors, such as the mourner's resilience and their social network [10]. Although it is possible to predict the risk for one to develop PG [11], screening is not a common practice. Furthermore, the development of PG often goes unnoticed by the widow/widower, who then also does not realize that she or he can benefit from help [12]. This has led to a situation in which older adults are unaware of their own needs, do not seek help, and do not receive the care they need.

A wide range of interventions are available for either preventing or treating PG including support groups, writing exercises, and individual psychological counseling. Internet-based options have also started to emerge (eg, [13-16]). Such interventions mostly consist of writing exercises with minimal therapist involvement. A recent evaluation of an internet-based, preventive intervention shows a moderate to large reduction in the duration of grief, depression, anxiety, and psychopathological distress [17]. In general, however, the evidence on the effect of online preventive interventions remains inconclusive.

In this proposal and the upcoming project LEAVES, we will develop, implement, and evaluate an online bereavement support program that will support the prevention and treatment of PG. In parallel, we will develop an exploitation strategy for the service, so that it can persist on a sustainable model following project completion.

LEAVES Online Bereavement Support Service

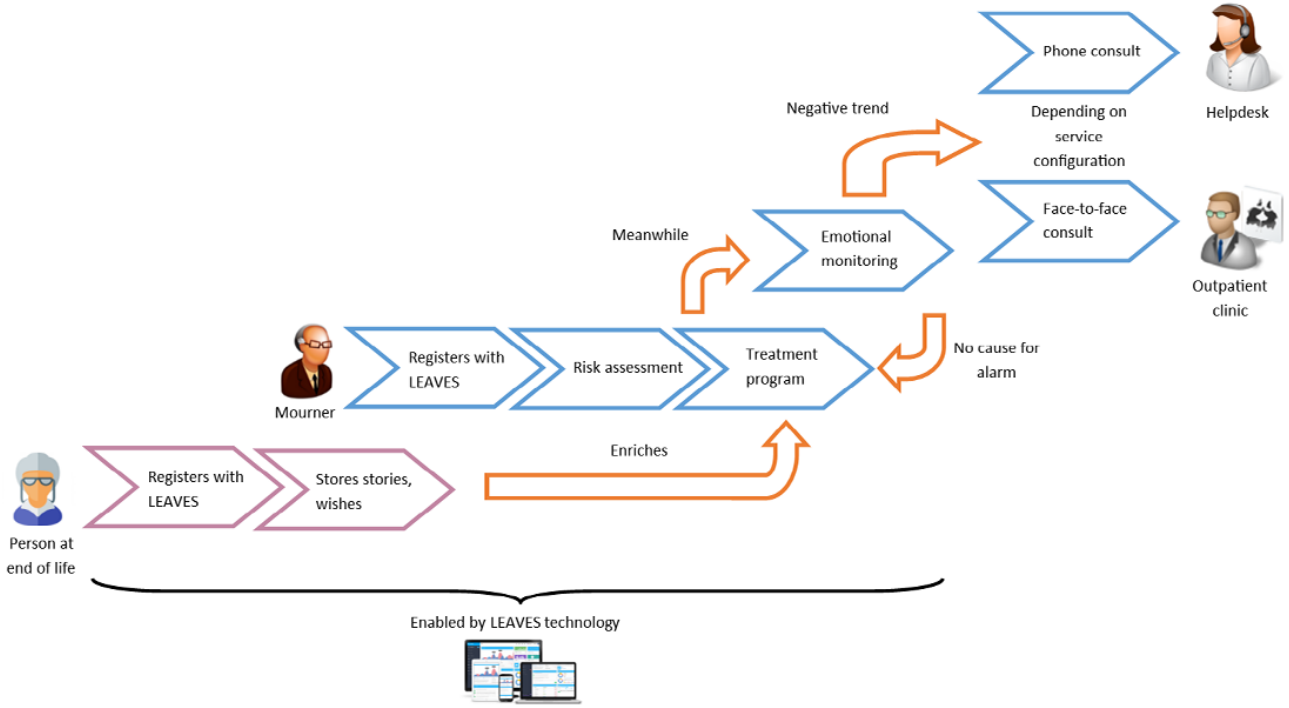
> *Mary receives an email from LEAVES. LEAVES offers her the option to be guided throughout her mourning process.*

The LEAVES service will provide support to older adults who have lost their spouse, helping them cope with their grief, by preventing PG or treating PG once detected. Ultimately, the aim is to prevent depression or social isolation, strengthen resilience and well-being, and accelerate one's return to society. LEAVES helps older adults to process the loss of a spouse in an empathic and caring online environment. It can detect persons at risk for complications following loss of a spouse, reveal negative trends in the emotional life of the widow or widower, and intervene to counter such trends. The service will rely on online treatment whenever possible but will be blended with telephone or face-to-face counseling when necessary.

The LEAVES value chain (Figure 1) begins when a person at the end of their life is presented with the LEAVES service, for example, by an elderly association (as a service to their members) or a funeral home (as part of their service package). Once the person using the service passes away, the mourning spouse is automatically invited to the service. Alternatively, those in mourning can register for the service without prior participation of the deceased spouse. After registering with the service via the LEAVES website, a user profile is created for each individual. This profile includes demographics (for

personalizing the service) and a risk assessment for developing PG based on an online survey founded upon scientific risk prediction models. The mourner then enters the treatment pipeline, which is based on the LIVIA program [17,18]. LIVIA focuses on guiding mourners during marital bereavement via a self-service, online program. Online treatment is supported by stories and memories, provided by the person who passed away via the Before You Leave service [19]. To facilitate the interaction between technology and mourner, the LEAVES service will make use of a conversational agent-based interaction paradigm, in which the user interacts through natural language with a virtual on-screen character, an approach that is gaining popularity in health-related applications (eg, [20,21]). Using this technology, a caring, empathic, and individually tailored online environment will be developed to foster trust and compliance. The mourner's emotional state will be constantly monitored both by assessing the user's responses during dialogue interactions with the virtual agent and by experience sampling methods (ie, short, periodic Q&A modules), offered via tablet or mobile platforms. If any negative trend is observed indicating potential risk for PG, the mourner will be directed toward LEAVES' offline services (eg, phone helpdesk, face-to-face meetings). The service will be developed around the notion that *the user will be helped online when possible, but offline when necessary*.

Figure 1. LEAVES (optimizing the mentaL health and resiliencE of older Adults that haVe lost thEir spouSe via blended, online therapy) value chain.



The LEAVES service focusses on the following target groups:

- Primary end users: Older adults (65+) who have recently lost their spouse. The service will enable them to properly cope with the associated life changes.
- Secondary end users: Those close to the mourning spouse (eg, children, neighbors, and friends). They are concerned about the mourner's situation but may find it hard to estimate his or her emotional state if the mourner remains emotionally closed about the subject. LEAVES can assist by encouraging transparency in the situation.
- Secondary end users: Deceased spouse. Before passing away, one may be concerned about the future of their spouse and his/her ability to cope with the new situation. LEAVES allows them to store their stories and wishes, thereby creating a lasting memory that will ease the mourning process of those left behind.
- Secondary end users: Clinical professionals. They will receive fewer patients suffering from PG. Those who do suffer from PG will seek assistance at an earlier stage.
- Lead users: Undertakers. They offer the service as part of their service package, thereby gaining a competitive advantage.
- Lead users: Elderly associations. They can offer the service as part of their services for their members.

Consortium

The project consortium consists of a collection of organizations including research, end user, and clinical organizations; small- and mid-sized enterprises; and a large enterprise. The project is led by Roessingh Research and Development (RRD). Service model design and visual design are mainly being taken care of by The Dutch National Foundation for the Elderly (NFE) and the Swiss SME Nothing AG (NTH). Technology development is being led by RRD. RRD has created a solid foundation for an electronic health (eHealth) platform and AI dialogue systems in numerous European and commercial projects. NTH will complement these skills with their functional front-end and graphical user interface design skills. The University of Bern, Switzerland (UoB), the School of Social Work of the University of Applied Sciences and Arts in Olten, Switzerland (SSW), and the Psychiatric Department at the Health Unit of Baixo Alentejo,

Portugal (ULSBA), bring in their vast and extensive experience and knowledge of treating PG, and their skills in leading clinical evaluations. NOVA University of Lisbon (UNL) will bring in their expertise on testing and validating technological tools for health intervention, as well as economic evaluation and cost-effectiveness analysis. The Dutch insurer and funeral undertaker DELA Natura- en levensverzekeringen (DELA) will contribute with expertise from the innovation department, where they continuously seek new ways to support their clients around end of life, both online and offline. Finally, the Portuguese SME Sensing Future Technologies (SFT) will utilize their experience in marketing eHealth technologies for the Portuguese and international markets.

Methods

Core Technology Components

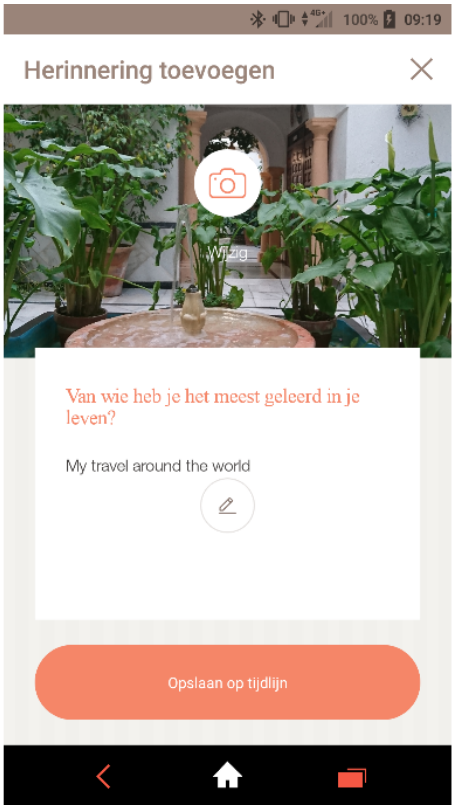
The core technology components in LEAVES are the mobile app Before You Leave (technology readiness level [TRL] 9, developed by DELA), the Livia Online Grief Program (TRL 7, developed by the UoB), and the natural language-based Virtual Agent Platform (TRL 7, developed by RRD). All modules will receive an accessible design and a clean user experience given the subject matter of coping with grief (furnished by NTH).

Before You Leave

> *After being notified about the LEAVES app by his caretaker, Frank downloads the LEAVES app on his tablet in order to leave Mary with memories. He opens the app and chooses a conversational agent to his liking: Peter. This agent questions Frank about defining moments in his life, his values, and wishes for after he passes away.*

The mobile app "Before You Leave" (Figure 2) offers those with a terminal condition the option to store memories, personal information, messages to relatives, and personal wishes about how to deal with personal affairs after passing away. The user is guided through a documentation process via an automatized chatbot and cue cards, each providing a question (out of a total of 500+ cues). The app allows users to store audio, pictures, and video for each question. After the event of death, relatives of the deceased can access this information in order to have a repository of personal information about the deceased and to be able to refer to the deceased's wishes when faced with decisions about handling the deceased's affairs. At the moment of writing, the Before You Leave service is not available anymore, as the value proposition turned out not to correspond with the envisioned end-users' needs. The content and functionality of the service can be valuable for enriching the LEAVES service by allowing mourners to reflect on their life with their partner through the cues and other functionalities. This will be incorporated into the LEAVES service model and technology.

Figure 2. Before You Leave screen where a person is asked to reflect on whom they have learned most from in life.



The LIVIA Online Grief Self-Help Program

> *Interested, Mary signs up [in LEAVES] using her tablet and is first asked a set of questions. By answering these questions, the LEAVES service learns what type of mourner Mary is, so that it can adapt its content to best connect with her.*

The online self-help program LIVIA (Figure 3) addresses older adults who experienced divorce or marital bereavement greater than 6 months prior and who seek help for coping with PG symptoms, psychological distress, or adaptation problems in daily life. LIVIA has been developed and evaluated as a stand-alone guided self-help program [17,18]. The intervention is based on the task model of mourning [22] and the dual-process model of coping with bereavement [23]. LIVIA employs standard cognitive behavioral techniques for behavioral activation and modifying dysfunctional thoughts. In addition, writing tasks are used to clarify the meaning of the loss. Cognitive behavioral techniques are also used for identifying and activating intrapersonal and social resources, improve emotion regulation skills, and increase loss-related coping self-efficacy. This intervention aims to foster resilience, defined as the capacity to cope with the stressors related to the loss and adapt to a life without the spouse. A detailed description of the intervention can be found elsewhere [17,18].

Figure 3. Online grief self-help program LIVIA.

LIVIA consists of 10 text-based sessions, and includes (1) information about interpersonal loss and an assessment of the current personal situation; (2) exposure and loss-oriented interventions, such as writing tasks for accepting memories and pain, and addressing unfinished business; and (3) resources and restoration-oriented interventions for fostering positive emotions and thoughts, self-care, creating a new life without the partner, and promoting positive social relationships. In its current form, guidance includes 1 short, weekly email. In addition, participants can contact their coaches via a contact button for further support. LIVIA has demonstrated significant improvements in reducing grief, depression, psychopathology, loneliness, and embitterment [17].

The RRD Virtual Agent Platform

> *Mary also interacts with the LEAVES service via a conversational agent. She chooses a virtual agent named Wendy from a set of options. Wendy informs Mary about the phases that she is going through, answers her questions, and asks her to do exercises (eg, reflecting on a difficult period). Wendy regularly presents Mary with memories or stories that Frank provided to his conversational agent, Peter. Every 2 weeks, Wendy also asks Mary how she is doing via a few short questions on the LEAVES smartphone app.*
>
> *From the conversations with Mary, Wendy infers Mary's emotional state and adapts its content.*

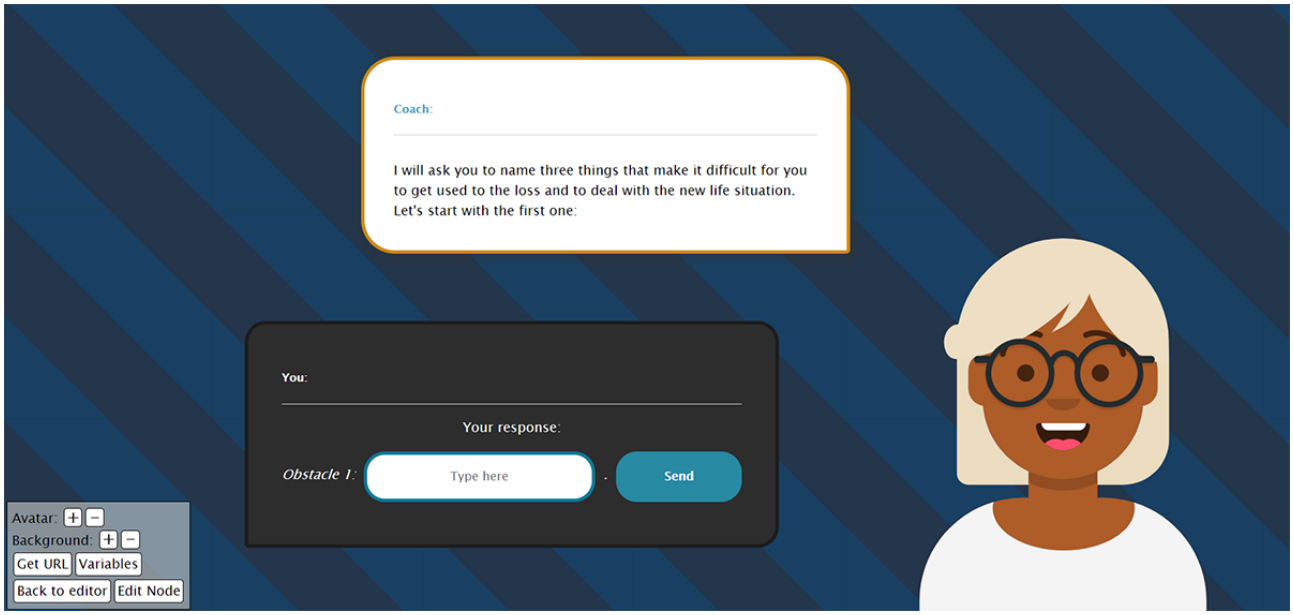
The RRD Virtual Agent platform is part of the back end of the LEAVES platform and consists of a set of tools and services that enables the creation and execution of dialogue-based natural interaction interfaces with end users. The platform is used to develop personal virtual agent companions in the context of eHealth apps that allow users to have tailored, dynamic conversations with a virtual agent. A core component of the platform is the WOOL Dialogue Framework, a simple, powerful dialogue framework for creating virtual agent conversations and completely open source licensed under an MIT License. More information and the tool itself can be found on the WOOL website [24]. The WOOL framework consists of 3 main components: (1) the dialogue language definition, (2) an easy-to-use editor for creating dialogue scripts, and (3) a set of tools to execute these dialogues. The WOOL Dialogue Framework was created in the context of the Council of Coaches project, a research and innovation project funded by the European Commission's Horizon 2020 Research Programme.

The RRD Virtual Agent platform was designed to provide tailored motivational advice on various health domains and is grounded in theory on tailoring health communication [25] and providing motivational support in the physical activity promotion domain [26]. The screenshot in Figure 4 shows an

example virtual agent, demonstrating how a simple natural language interaction is achieved using a text-based user interface and allowing the user to choose his/her replies from a pregenerated list. The core technology platform consists of dialogue authoring tools and a client–server architecture for executing the tailored dialogues.

The content in LEAVES will be offered by the virtual agent in "bite-sized" chunks and expressed in natural "conversational" style, making the contents of the service more accessible.

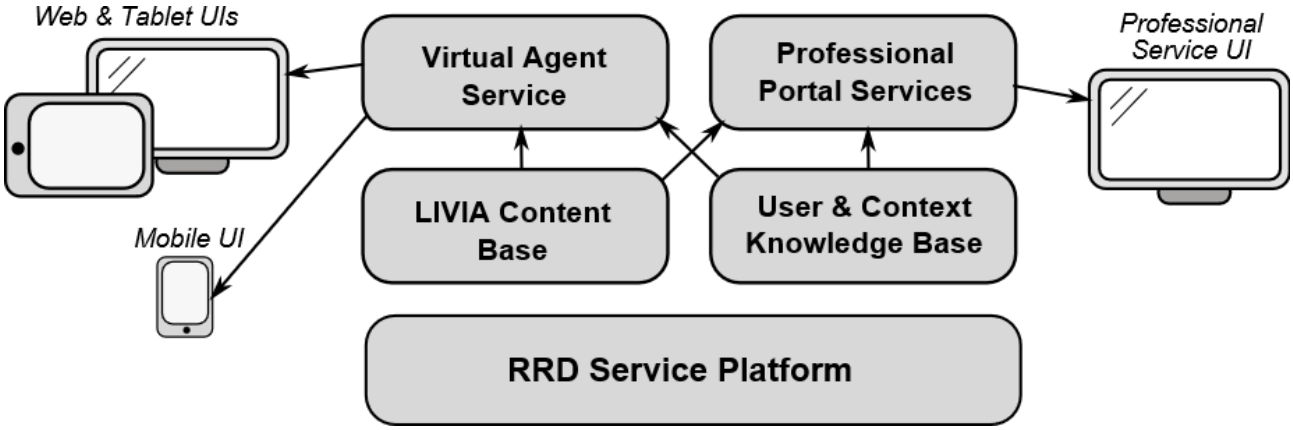
Figure 4. Example virtual agent "Anja" asking for input from the user on obstacles faced to deal with the loss of a partner.



The LEAVES Platform Architecture

Figure 5 outlines the component overview for the LEAVES platform. The RRD Service Platform forms the basis for user management and secure data storage and access, and also provides APIs to the virtual agent service and professional portal services that serve the various core LEAVES user interfaces. Input to the platform is provided through the Before You Leave Service and LIVIA Content Base.

Figure 5. LEAVES (optimizing the mentaL health and resiliencE of older Adults that haVe lost thEir spouSe via blended, online therapy) service component overview. UI: user interface.

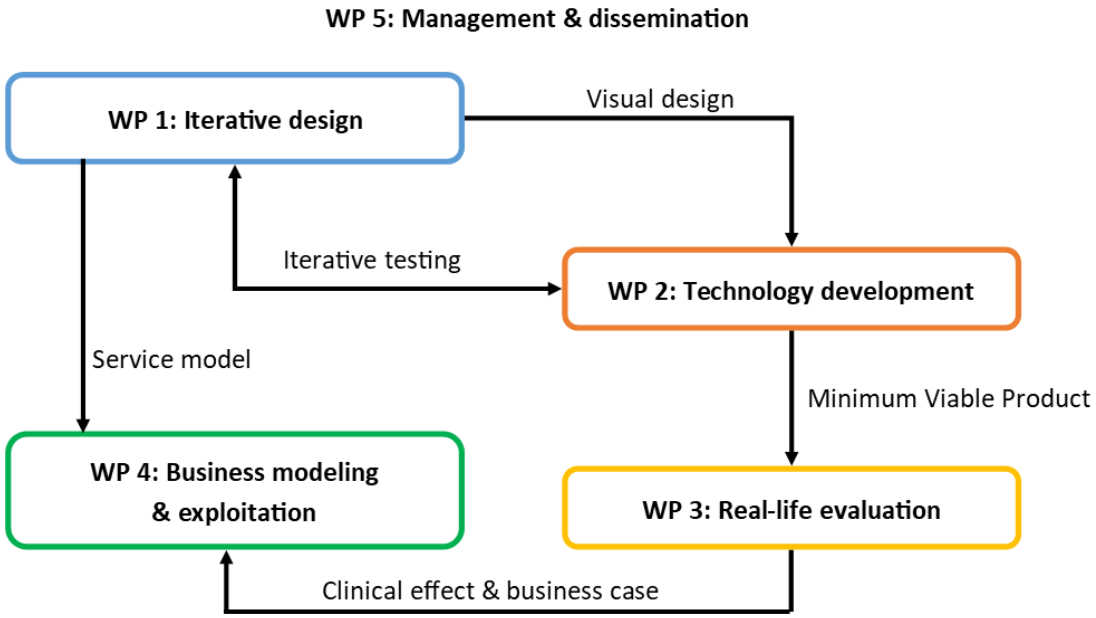


Workplan

The workplan of the LEAVES project is divided into the 5 work packages illustrated in Figure 6: (1) iterative design, (2) technology development, (3) real-life evaluation, (4) business modeling and exploitation, and (5) management and dissemination.

The first 2 years of the project will focus on the design and development of the LEAVES platform and its service model. These activities are mostly handled in work packages 1 and 2.

Figure 6. LEAVES (optimizing the mentaL health and resiliencE of older Adults that haVe lost thEir spouSe via blended, online therapy) work package (WP) overview.



The objective of the first work package (ie, iterative design) is to make sure that the service, tools, and user interface design are in line with the expectations of all end-user groups of the LEAVES service. Several multidisciplinary design workshops will take place in which a wide array of techniques from user-centered design will be employed, including user story mapping, interviews, definition of "jobs to be done," focus group discussions, information architecting, persona definitions, and card sorting for content aggregation. The results of these procedures will lead to first sketches and wireframes of the interface and its interactive experience. The user interface will be crafted with careful attention to accessibility standards, considering the specific needs of the elderly in user experience and user interaction. Iterative evaluations with different prototypes (with low, medium, and high fidelity) will be performed with example members of the target group. For the low- and mid-fidelity prototype evaluation, a series of fairly detailed mock-ups will be available, providing simulated interactive functionality and navigation. The prototypes will be presented to the users in a controlled laboratory environment, and the evaluations will be conducted in different iterative cycles with usability experts. Before the final pilot, an extensive usability study will be performed to make sure that all aspects are usable within the evaluation.

The second work package (ie, technology development) deals with all technology developments needed to realize a stable platform to be used in the real-life evaluation. To do so, the technology partners will work together setting working prototypes to maximize the impact of the iterative design work in the first work package. Technical and clinical partners will work together to translate the plain text content of LIVIA and Before You Leave into dialogue-based text. This work package will also deal with the personalization of the content to specific end users based on user profiles. A continuous personalization of the service will be performed as a response to the emotional assessment performed in the platform. Last but not least, this work package will ensure that the content system will be designed with a "privacy by default" approach. In the LEAVES project, we will go beyond the state of the art in privacy design and will include a personal data control interface that allows older adults (with relatively undeveloped technological skills and low awareness of privacy control) to control the access and storage of their personal data. Given the sensitive nature of the treatment and the data that are collected about the individual who uses the LEAVES service, ensuring privacy and control over personal data has top priority.

The third and last year of the project will be mostly dedicated to real-life evaluation, refinement of the business model, and exploitation. The third work package (ie, real-life evaluation) focuses on the evaluation of the clinical and economic potential of the LEAVES service by conducting a longitudinal real-life evaluation across 3 countries: Portugal, the Netherlands, and Switzerland. This work package concerns the development of the study protocol as well as the clinical evaluation (in Portugal and Switzerland) and acceptance of technology and service design (in the Netherlands). Finally, an economic evaluation will be performed by determining the differences in costs and the health benefits that result from the use of LEAVES.

The clinical evaluation will involve older adults (65+) who express the need for help in mourning their spouse and will focus on well-being (eg, a decrease in grief symptoms measured with the Texas Revised Grief Inventory [27]; loneliness, as assessed with the De Jong Gierveld Short Scale for Emotional and Social Loneliness [28]; and improved quality of life measured with the Satisfaction with Life Scale [29]) and end-user satisfaction. Results will be compared with those obtained in the same timeframe from people that are "regular mourners" (in The Netherlands), and in a waiting control group (in Switzerland and Portugal). Next, close ones to older adults and care professionals will be consulted on potential effects of the service, to gather a comprehensive overview. Exit strategies will be put in place for participants who need additional care

or want to stop using the service. The objective of the economic evaluation is fourfold and will aim to assess the financial consequences from implementing the LEAVES service. It will (1) estimate the change in symptoms averted with the implementation of LEAVES; (2) evaluate the costs associated with the implementation of LEAVES; (3) evaluate the avoided costs related to minimization of the grief symptoms; and (4) compare the costs of LEAVES with the benefits of implementing it, in terms of improved health.

The fourth work package (ie, business modeling and exploitation) concerns the development of a business model, integrated and supported on the evidence from the field, as well as a go-to-market strategy and commercial exploitation of the project output.

The fifth and final work package (ie, management and dissemination) concerns project management and ensures that the project will be executed on time, within budget, and with outstanding quality. Within this work package a dissemination and communication strategy is also defined and executed. Finally, the ethical guidelines for the project will be established, including procedures for medical ethical permission and informed consent, as well as project-wide methods for data handling (in a General Data Protection Regulation [GDPR]-compliant manner).

Results

The project runs from February 1, 2020, to January 31, 2023. Results of the project will be reported continuously following a dissemination and communication plan developed in the first year of the project. The dissemination plan follows annual goals: (1) create awareness about the concept, (2) stimulate involvement, and (3) facilitate exploitation. End users, potential lead users, the business community, researchers, and the general public are foreseen as prospective target groups.

Discussion

> *After 3 months, Mary feels ready to move on. This is confirmed by an online screening administered by Wendy that assesses Mary's resilience, self-sufficiency, loneliness, and happiness. Mary unsubscribes from the LEAVES service and deletes the app from her phone.*

In this proposal, we have described the development, evaluation, and exploitation of an online service that has the primary aim to prevent or treat PG among older adults who have lost their spouse. The project will innovate by developing a blended, virtual agent–based bereavement support program, in contrast to existing grief programs that rely mostly on text-based interventions. Robust monitoring mechanisms for detecting the onset and escalation of PG will be developed. Finally, the technology will be implemented and tested in 3 countries to ensure a pleasant user experience, gauge its effect, and determine its cost-effectiveness. Guaranteeing follow-through, the LEAVES consortium will work toward successful exploitation of the service.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Review of the LEAVES proposal.
[PDF File (Adobe PDF File), 71 KB - resprot_v9i9e19344_app1.pdf]

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Abbreviations

DSM: Diagnostic and Statistical Manual of Mental Disorders
ICD: International Classification of Diseases
LEAVES: optimizing the mentaL health and resiliencE of older Adults that haVe lost thEir spouSe via blended, online therapy
NFE: Dutch National Foundation for the Elderly
NTH: Swiss SME Nothing AG
PG: prolonged grief
RRD: Roessingh Research and Development
SFT: the Portuguese SME Sensing Future Technologies
SSW: School of Social Work of the University of Applied Sciences and Arts in Olten, Switzerland
TRL: technology readiness level
ULSBA: Psychiatric Department at the Health Unit of Baixo Alentejo, Portugal
UNL: University of Lisbon

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Proposal

Improving Adherence to Adjuvant Hormonal Therapy Among Disadvantaged Women Diagnosed with Breast Cancer in South Carolina: Proposal for a Multimethod Study

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Abstract

Background: Current clinical guidelines recommend that hormone receptor–positive breast cancer survivors take adjuvant hormonal therapy (AHT) for 5 to 10 years, following the end of definitive treatment. However, fewer than half of patients adhere to the guidelines, and suboptimal adherence to AHT is associated with an increased risk of breast cancer mortality. Research has extensively documented sociodemographic and disease-specific factors associated with adherence to AHT, but very little evidence exists on behavioral factors (eg, knowledge, patient-provider communication) that can be modified and targeted by interventions.

Objective: The goal of this study is to develop and test a theory-based, multilevel intervention to improve adherence to AHT among breast cancer survivors from racially and socioeconomically disadvantaged backgrounds (eg, Medicaid-insured). The specific aims are to (1) explore multilevel (eg, patient, health care system) factors that influence adherence to AHT; (2) develop a theory-based, multilevel intervention to improve adherence to AHT; and (3) pilot test and evaluate the intervention developed in Aim 2.

Methods: For Aim 1, we will recruit breast cancer survivors and health care professionals to participate in semistructured interviews to gain their perspectives about barriers and facilitators to AHT use. We will conduct a directed content analysis of the Aim 1 qualitative interview data. For Aim 2, we will integrate Aim 1 findings and current literature into the design of a

multilevel intervention using an Intervention Mapping approach. For Aim 3, we will recruit Medicaid-insured breast cancer survivors to assess the feasibility of the pilot intervention.

Results: From May 2016 to July 2018, we completed interviews with 19 breast cancer survivors and 23 health care professionals in South Carolina. We will conduct a directed content analysis of the qualitative interview data. Results from this analysis will be used, in combination with current literature, to design (Aim 2) and pilot test a theory-based multilevel intervention (Aim 3) in Summer 2021. Results of the pilot are expected for Fall 2021.

Conclusions: This study will provide a deeper understanding of how to improve adherence to AHT, using a novel and multilevel approach, among socioeconomically disadvantaged breast cancer survivors who often experience disproportionate breast cancer mortality.

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breast neoplasms; medicaid; medication adherence; vulnerable populations; hormonal therapy; endocrine therapy; qualitative methods

Introduction

Background

Adjuvant hormonal therapy (AHT) has been shown to significantly reduce recurrence and mortality rates among women diagnosed with hormone receptor–positive (HR+) breast cancer [1]. Current clinical guidelines for women diagnosed with early stage (stages I-III) HR+ breast cancer recommend up to 10 years of AHT with tamoxifen or an aromatase inhibitor (AI), following surgery, chemotherapy and/or radiation, as indicated. [2,3]. However, although AHT is considered the standard of care for breast cancer, reports show that only about 50% of women complete treatment as recommended [4,5].

Systematic reviews show that sociodemographic factors, such as race and age, are associated with treatment adherence. In contrast, there is limited evidence about psychosocial or behavioral factors that could be targeted with interventions [4,6,7]. Additionally, previous studies that have examined modifiable factors suggest that negative beliefs about AHT, limited social support, low decisional balance scores and poor patient-provider communication are all negatively associated with therapy adherence [8-12]. Early discontinuation of and poor adherence to AHT have been significantly associated with disease progression and increased morality rates [5,13].

The problem of suboptimal adherence to AHT is important for three key reasons. First, roughly 75% of diagnosed breast cancers are HR+ [14], meaning that adherence to AHT is critical for extending the survival of the majority of breast cancer survivors. Second, studies show that differences in treatment, including AHT use, significantly contribute to persistent racial disparities observed in breast cancer mortality rates between Black and White women [15,16]. This disparity increases for women who are socioeconomically disadvantaged [17,18]. Third, rates of adherence to AHT are lowest among financially disadvantaged populations versus other population–based groups. For example, only 58% of Medicaid-insured women adhered to AHT in the first year [19], compared to 80%-85% in privately insured populations [20,21]. Hershman et al [22] recently found that low annual household income (<US $40,000) significantly decreased the odds of Black women adhering to AHT compared to White women. Therefore, the improvement of adherence to AHT among socioeconomically disadvantaged Black women with breast cancer is critical to increase their survival rate as well as to close the gap on racial disparities in breast cancer treatment.

Project Goal and Innovation

The overall goal of this study is to improve adherence to AHT among breast cancer survivors from racially and socioeconomically disadvantaged backgrounds. The specific aims of this study are as follows: (1) explore patient, health care system, and structural factors that may influence adherence to AHT; (2) develop a theory-based, multilevel intervention program to improve adherence to AHT; and (3) pilot and evaluate the intervention program designed in Aim 2.

This project will incorporate principles of health communication theory into the development and testing of the proposed multilevel intervention program. The field of health communication has been nationally prioritized as a strategy to improve individual and population health [23]. Health communications reflect an ecological perspective which posits that individual health beliefs and behaviors are influenced by the broader social environment. Thus, effective public health communication can improve health behaviors by using strategies that consider multiple levels of influence (eg, intrapersonal, interpersonal, community) [24]. The use of health communication theory in this study represents a novel approach to fill a gap in the literature on how to apply theory in multilevel interventions. Furthermore, the application of theory will yield a practical framework for how to use health communication theoretical constructs to determine appropriate communication strategies (eg, knowledge, attitudes) that will target factors at multiple levels known to influence AHT adherence, and how to test them in a multilevel intervention.

Methods

Study Overview

This project received funding from the National Cancer Institute of the National Institutes of Health (2015-2020). The proposed research will address concepts proposed by the World Health

Organization's (WHO) Multidimensional Adherence Model Framework [25] and the Multi-level Context of Cancer Care Model [26] (Table 1). This adapted framework shows how factors are nested within multiple levels to influence AHT adherence and can be useful for designing and targeting multilevel interventions. The formative, in-depth, semistructured interviews (Aim 1, Years 1-2) will constitute the basis for the development of culturally appropriate messaging and content of the multilevel intervention (Aim 2; Year 2) to be pilot-tested and evaluated in Year 3 (Aim 3).

Table 1. Modifiable factors at multiple levels that influence adherence to adjuvant hormonal therapy [27-29].

Level and factors	Related factors	Potential interventions
Patient	• Psychosocial factors	• Education + behavioral support
	• Knowledge, beliefs, attitudes	• Case management
	• Illness perceptions	• Pharmacist-led, multicomponent intervention
Family/social support	• Family dynamics	• Family/dyadic education
	• Friends, network support	
	• AHT recommendations	• Enhance skill mix/competencies of care team
Health care system/health care team	• AHT fill interval	• Reminders
	• Communication preferences/styles	• Education on effective patient-centered communication + behavior management
	• Perceptions/bias	
	• Cost of AHT	• Reduced out-of-pocket expenses
Policy/structural/cultural	• National/state/local policy	• Public health insurance coverage
	• Distance to health/pharmacy services	

Aim 1. Explore Patient, Health Care System, and Structural Factors That May Influence Adherence to AHT

Study Design

Study Aim 1 will explore patient, health care system, and structural factors that influence adherence to AHT (Years 1-2). To achieve this aim, in-depth, semistructured qualitative interviews will be conducted with health care professionals who work in oncology settings and with breast cancer survivors. For purposes of this research, we define a "breast cancer survivor" as anyone who has been diagnosed with invasive breast cancer.

Health Care Professional Recruitment and Eligibility

Health care professionals will be recruited to participate in qualitative interviews. The study will target health professionals from key networks and organizations in South Carolina, including professional organizations (eg, oncology nursing, oncology social work), cancer centers and South Carolina's cancer coalition and department of health. The primary method of recruitment will be through email invitation letters sent by the study's principal investigator (PI).The invitation letter will describe the study aims, study procedures, funding source, and institutional review board approval protocol information. Interested health care professionals will be able to contact the study PI directly by telephone or email. The PI will schedule an interview at a time and location convenient to the potential participants to determine their eligibility for the study. Eligibility requirements will include (1) being employed as a health care professional (ie, physicians, nurses, pharmacists, social workers, patient navigators); (2) currently working with breast cancer patients, for example in an oncology setting, such as a cancer center or hospital; and (3) age ≥ 21 years.

Health Care Professional Data Collection

Before the interview, health care professionals will be asked to complete a brief questionnaire about their personal (eg, gender, age) and professional (eg, current job title, type of health care professional, health care setting) information. The PI will conduct all interviews using a guide developed by the study team. Key topics include: (1) major barriers to AHT adherence; (2) organizational resources to support posttreatment (eg, surgery, chemotherapy) of breast cancer survivors; (3)

communication among health care team members; (4) communication with patients and their families; and (5) organizational strategies for addressing problems with AHT adherence. Participants will receive a US $50 cash stipend for their time and effort. At the end of the interview, participants will be asked for their contact information if they are willing to participate in a follow-up feedback session, which will serve to inform the development of a subsequent intervention. All interviews will be digitally recorded and field notes will be taken.

Breast Cancer Survivor Recruitment and Eligibility

Breast cancer survivors will be recruited from the South Carolina Oncology Associates (SCOA) and the Gibbs Cancer Center and Research Institute (GCCRI). Eligibility requirements include: (1) age≥21 years; (2) diagnosed with HR+, invasive breast cancer; (3) having medical records that confirm the prescription of any hormonal treatment (anastrozole, exemestane, letrozole, tamoxifen) at any point after diagnosis; (4) eligible for or enrolled in South Carolina Medicaid program; and (5) being able to speak and read in English.

To recruit participants, we will apply a recruitment model developed by Heiney and colleagues [30], which combine social marketing with relationship building. The PI and a research assistant will work with SCOA and GCCRI staff to identify participants who meet the study eligibility criteria using electronic medical records. SCOA patients will be mailed a personal invitation letter from the PI explaining the goals of the study, including a Frequently Asked Questions document that addresses potential concerns of research participants. The letter will include a phone number to call if the participant prefers not to be contacted. Within 3-5 days after the recruitment letter is mailed, the PI or research assistant will contact the participant by phone to provide them with an overview of the study. If the participant expresses interest in the study, the PI or research assistant will verify the participant's study eligibility. If eligibility is met, an interview appointment will be scheduled at a time and location convenient to the participant. If a participant is not eligible, the PI or research assistant will let the participant know that they did not meet the study criteria and will thank them for their interest in participating.

At GCCRI, designated staff will contact potentially eligible breast cancer survivors by phone and provide them with an overview of the study. If the participant shows interest in the study, GCCRI staff will then ensure the participant meets study eligibility. If eligibility is met, GCCRI staff will request verbal consent by phone and set up an interview appointment at GCCRI. Interested and eligible participants will be mailed an "Appointment Form" confirming the date, time, and location of the interview; a copy of the informed consent; and the Frequently Asked Questions document.

Breast Cancer Survivor Data Collection

Interviews with participants recruited from SCOA will be scheduled and conducted at a location (eg, home, library) and time convenient to the participant, while GCCRI participant interviews will be scheduled in person and onsite at GCCRI. Before the interviews, the following informed consent process will be conducted: a research team member (PI or research assistant) will read aloud a consent form that will inform the participant about the following components of the study: title of the research project, the identity of the project PIs and their respective contact information, an introduction about the study, the aims of the study, reason for the project, a summary of why the individual has been asked to participate, a description of the study procedures (ie, audiotaping of interviews), an outline of any risks and/or benefits, an overview of how confidentiality will be maintained, a discussion of any benefits, and a method of securing additional information or asking questions. After the consent form is read aloud and the participant agrees to participate in the study, the research team member and participant will sign and date the form. Participants will be given a copy of the form for their records.

Following consent, participants will be asked to complete a brief information form about their personal information (eg, age, race, marital status), hormonal therapy (eg, type of drug, daily use), and type of AHT resources used and preferred. The research team will conduct all interviews using a semistructured interview guide. Breast cancer survivors will be asked to describe their experiences with AHT, including experiences communicating with health care professionals about AHT, and strategies used for addressing AHT nonadherence. All participants will be given a US $50 cash stipend for their time and effort. At the end of the interview, participants will be asked if they are willing to participate in the intervention development phase of this study (Aim 2).

Data Analysis of Interviews

All interviews will be recorded and transcribed verbatim by a professional transcription service. Each participant's audio file and transcript will be assigned the same unique identifier as their corresponding brief questionnaire. Quality control checks will be conducted while reviewing the transcripts to ensure that no personal identifiers are used. Audiotaped transcripts and field notes will be used for data analyses. Transcripts will be independently read and reviewed to check for accuracy and authenticity.

To identify potential modifiable factors and future intervention targets for Aim 2, Assarroudi et al's [31] qualitative content analysis approach will be used to analyze interview transcripts. The PI will develop a preliminary codebook of main categories and subcategories derived from the WHO Multidimensional Adherence Model Framework [25] and Multilevel Context of Cancer Care [26]. The PI will work with other team members to discuss the codebook as well as the final main categories and subcategories and their related meanings. The PI and two other research team members will independently read and code a selection of transcripts using the preliminary codebook. Following this initial coding, all team members will meet, compare coding results, and discuss differences in coding interpretations and concerns with the preliminary codebook. The PI will revise the codebook as needed. Once the codebook is finalized, a research assistant who is knowledgeable in the study topic area will, independently, code all the transcripts, and the PI will code a random sample of the transcripts. The PI and research assistant will then meet and discuss coded

transcripts, reach a consensus among any discrepancies and calculate intercoder agreement [32].

Aim 2. Develop a Theory-based, Multi-level Intervention Program to Improve Adherence to AHT

Overview of Intervention Development Via Data Integration/synthesis and Intervention Mapping

Multiple sources will be used for the development of a theory-based, multilevel intervention program, including findings from Aim 1, current scientific literature, insights from participant feedback sessions (described below), and expertise of the project mentoring team. After analyzing the qualitative data from the breast cancer survivor and health care professional interviews, we will develop a modified, data-informed logic model of potential interventions aimed at health care professionals and their organizations, and survivors and their family/social support. Logic models, representing an outcomes hierarchy, will assist with a broad understanding of the components of each potential intervention [33]. Potential intervention strategies are shown in Table 1 [27-29]. The research team will systematically review and compare findings from the survivor and health care professional qualitative interviews and quantitative questionnaire data. Of interest is not only the variation within the survivor and health care professional groups, but also the variation between the survivor and health care professional reports. We will, therefore, identify themes that occur within and across groups. We will employ a logic model based on the PRECEDE approach [34] to illustrate survivors' experiences with AHT and how knowledge, perceptions and attitudes at different levels impact their ability to adhere to AHT. We will apply appropriate multi-level theories to refine the intervention strategies and messages [35-37].

Validation of Formative Data and Intervention Design Through Participant Feedback Session

From the group of participants that agreed to participate in a follow-up feedback session, we will select a purposive sample of breast cancer survivors (n=5; and their designated family member/friend, n=5) and health care professionals (n=5), based on their brief questionnaire and interview responses. We will host two, 1 to 2 hours feedback sessions: one for breast cancer survivors and their family member/social support, and another one for health care professionals. The feedback sessions will provide participants with the opportunity to judge the accuracy and credibility of the qualitative research findings, as well as to provide alternative interpretations and explanations when necessary [38]. We will also discuss any differences of opinion that may appear between the survivor and health care professional interviews to reach a resolution. Participants will receive US $50 and a light meal for their time and effort upon completion of the session. The project mentoring team will provide guidance on how to refine the intervention design based on the data from the feedback sessions and resolve any data discrepancies.

Results

The institutional review boards of the University of South Carolina, Prisma Health (formerly Greenville Health System) and Spartanburg Regional Hospital System reviewed the study protocols for Aim 1 and determined that they were exempt from human research subject regulations. Qualitative data collection for Aim 1 began in May 2016 and has been completed as of July 2018. A total of 19 breast cancer survivors and 23 health care professionals have been interviewed. Qualitative data analysis will be completed by December 2020. Results from this analysis will be used, in addition to current literature, to design (Aim 2) and pilot test a theory-based multilevel intervention (Aim 3) by Summer 2021. Multiple sources will be used for the development of a theory-based, multilevel intervention, including findings from Aim 1, current scientific literature, insights from participant feedback sessions (Aim 2), expertise of the research team, and trainings from the Multilevel Intervention Training Institute at the National Cancer Institute.

Discussion

Findings from this research will help fill a gap in our current understanding of underlying modifiable factors that influence adherence to AHT, particularly among understudied disparate populations [4]. To our knowledge, no previous study has applied a multi-level intervention approach to improve adherence to AHT [39]. Applying this approach to the cancer treatment and survivorship phases of the cancer control continuum is novel because most multi-level research in this area focuses on prevention and screening [26,40]. There is a similar pattern within the field of breast cancer research, where there are fewer intervention studies that focus on improving breast cancer treatment outcomes, compared to screening [41,42]. Among the studies that focus on improving adherence to AHT, few have found significant intervention effects [39,43-45] or are currently analyzing data [46].

In conclusion, achieving the proposed aims will contribute to the scientific community's growing interest in multilevel intervention design and analyses; describe relationships between modifiable patient, family/social support, and health care system/team factors and adherence to AHT; and identify feasible intervention strategies for improving adherence to AHT among breast cancer survivors from racially and socioeconomically disadvantaged backgrounds.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
NIH peer reviews.
[PDF File (Adobe PDF File), 172 KB - resprot_v9i9e17742_app1.pdf]

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Abbreviations

AHT: Adjuvant hormonal therapy
GCCRI: Gibbs Cancer Center and Research Institute
HR+: Hormone receptor-positive
PI: Principal investigator
SCOA: South Carolina Oncology Associates
WHO: World Health Organization

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Protocol

Continuity of Care for Patients with Obesity-Associated Chronic Conditions: Protocol for a Multisite Retrospective Cohort Study

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Abstract

Background: Obesity affects nearly half of adults in the United States and is contributing substantially to a pandemic of obesity-associated chronic conditions such as type 2 diabetes, hypertension, and arthritis. The obesity-associated chronic condition pandemic is particularly severe in low-income, medically underserved, predominantly African-American areas in the southern United States. Little is known regarding the impact of geographic, income, and racial disparities in continuity of care on major health outcomes for patients with obesity-associated chronic conditions.

Objective: The aim of this study is to assess, among patients with obesity-associated chronic conditions, and within this group, patients with type 2 diabetes, (1) whether continuity of care is associated with lower overall and potentially preventable emergency department and hospital utilization, (2) the effect of geographic, income, and racial disparities on continuity of care and on health care utilization, (3) whether continuity of care particularly protects individuals at risk for disparities from adverse health outcomes, and (4) whether characteristics of health systems are associated with higher continuity of care and better outcomes.

Methods: Using 2015-2018 data from 4 practice-based research networks participating in the Southern Obesity and Diabetes Coalition, we will conduct a retrospective cohort analysis and distributed meta-analysis. Patients with obesity-associated chronic conditions and with type 2 diabetes will be assessed within each health system, following a standardized study protocol. The primary study outcomes are overall and preventable emergency department visits and hospitalizations. Continuity of care will be calculated at the facility level using a modified version of the Bice-Boxerman continuity of care index. Race will be assessed using electronic medical record data. Residence in a low-income area or a health professional shortage area respectively will be assessed by linking patient residence ZIP codes to the Centers for Medicare & Medicaid Services database.

Results: In 4 regional health systems across Tennessee, Mississippi, Louisiana, and Arkansas, a total of 53 adult hospitals were included in the study. A total of 147,889 patients with obesity-associated chronic conditions who met study criteria were identified in these health systems, of which 45,453 patients met the type 2 diabetes criteria for inclusion. Results are expected by the end of 2020.

Conclusions: This study should reveal whether health system efforts to increase continuity of care for patients with obesity and diabetes have potential to improve outcomes and reduce costs. Analyzing disparities in continuity of care and their effect on major health outcomes can help demonstrate how to improve care and use of health care resources for vulnerable patients with

obesity-associated chronic conditions, and within this group, patients with type 2 diabetes. Better understanding of the association between continuity and health care utilization for these vulnerable populations will contribute to the development of higher-value health systems in the southern United States.

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KEYWORDS

continuity of care; obesity-associated chronic conditions; disparity; obesity; diabetes

Introduction

Background

Obesity affects nearly half (40%) of adults in the United States [1,2] and contributes substantially to a pandemic of obesity-associated chronic conditions. Obesity commonly leads to multiple chronic conditions such as type 2 diabetes, hypertension, cardiovascular disease, cerebrovascular disease, and arthritis [3]. Our recent research shows that 34% of patients with obesity-associated chronic conditions in the midsouthern United States have diabetes. Projections indicated that 81 million adults will have multimorbidity by 2020, and obesity serves as an underrecognized root cause for this national pandemic of multimorbidity [4-7]. The pandemic of obesity-associated chronic conditions is particularly severe in low-income, medically underserved, and predominantly African-American areas in the southern United States.

Furthermore, the burdens of uncontrolled obesity-associated chronic conditions are rising nationwide, particularly in areas designated by the Human Resources and Services Administration as primary care health professional shortage areas of the southern United States [8-10]. The economic burden of adult obesity on the United States exceeds $215 billion [11]; the most common obesity-associated chronic conditions are known to increase health care resource utilization and costs [12-15]. Access to regular primary and specialty care is associated with improved chronic care management and reduces potentially preventable health care utilization attributed to obesity-associated chronic conditions [16,17]. Prior evidence from observational studies suggests that continuity of care is associated with higher medication adherence and lower health care resource utilization among older adults and patients with multiple chronic conditions [18-24]. But little is known regarding the impact of continuity of care for patients with type 2 diabetes or other obesity-associated chronic conditions in medically underserved areas of the southern United States.

There is a critical need to quantify the impact of geographic, income, and racial disparities on continuity of care and health care utilization and identify characteristics of health systems with higher continuity and lower health care utilization for patients with obesity-associated chronic conditions and type 2 diabetes. Effective population health improvement requires examining comprehensive data across health systems to look at variations in care. Such pragmatic research has the potential to translate best health systems practices across different communities in the southern United States.

Objectives

This protocol aims to assess (1) whether outpatient continuity of care is associated with lower overall and potentially preventable emergency department and hospital utilization for patients with obesity-associated chronic conditions and with type 2 diabetes, respectively; (2) the effect of geographic, income, ethnic, and racial disparities on continuity of care and overall and potentially preventable emergency department and hospital utilization among patients with obesity-associated chronic conditions and with type 2 diabetes; (3) whether continuity of care particularly protects individuals with obesity-associated chronic conditions and with type 2 diabetes at risk for geographic, income, ethnic, and racial disparities from overall and potentially preventable hospital and emergency department utilization; and (4) the characteristics of health systems with higher continuity and lower health care utilization for vulnerable patients with obesity-associated chronic conditions and in the type 2 diabetes.

We hypothesize that continuity of care will protect vulnerable individuals with obesity-associated chronic conditions, and within that group, individuals with type 2 diabetes, from overall and potentially preventable emergency department and hospital utilization. Additionally, continuity of care will be associated with lower emergency department and hospital use for (1) African-American individuals compared with that of white individuals or other individuals, (2) patients residing in health professional shortage areas compared with that of patients not residing in health professional shortage areas, and (3) patients residing in low-income areas compared with that of patients not residing in low-income areas. We also hypothesize that health systems with (1) a higher proportion of primary care providers to total providers, (2) a higher proportion of ambulatory to total encounters, and (3) a greater geographic distribution of ambulatory care sites will experience lower levels of overall and potentially preventable emergency department and hospital use among patients receiving ambulatory care within the system.

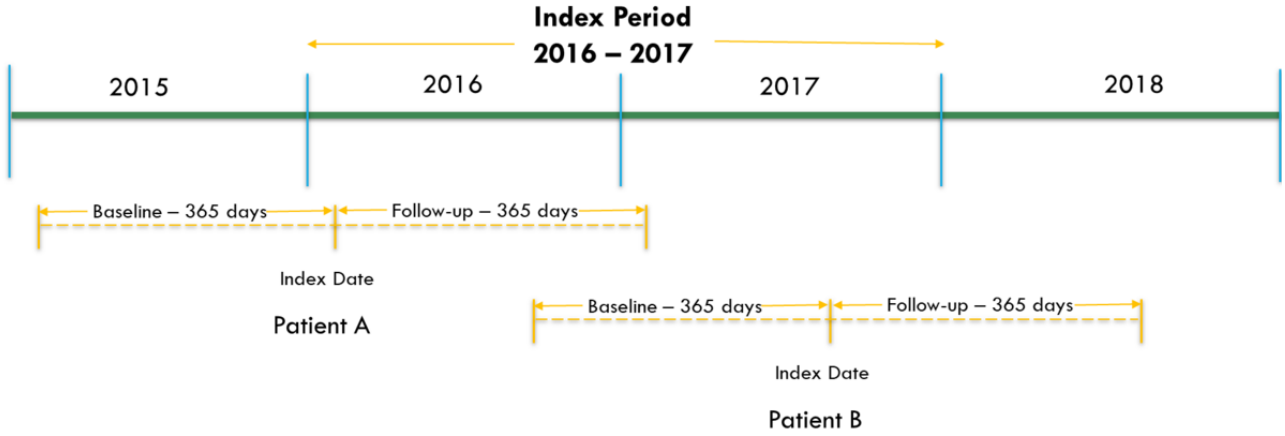
Methods

Study Design

We will conduct a retrospective cohort analysis and meta-analysis of all adult patients with obesity-associated chronic conditions—defined as patients who are obese (BMI≥30 kg/m^2) and who have ≥1 additional diagnosed obesity-associated chronic condition (a list of the included conditions is available in Multimedia Appendix 1) [25,26]—who are seen in health systems and practice-based research networks participating in the Southern Obesity and Diabetes Coalition.

This study will be conducted separately at the following sites: (1) University of Tennessee Health Science Center, (2) University of Mississippi Medical Center, (3) Tulane Medical Center, and (4) Ochsner Health System. The data from all sites will be aggregated to conduct meta-analysis. Electronic medical records from between 2015 and 2018 including encounters from all adult emergency department, hospitals, and clinics will be utilized. The index visit will be defined as the first visit of any type occurring between January 1, 2016 and December 31, 2017. The baseline year will be defined as the first full year prior to the qualifying index visit date (as defined above) for which the full inclusion criteria are met. The baseline year will be used to identify adult patients with obesity-associated chronic conditions and type 2 diabetes seen 2 or more times for ambulatory care. Outcomes will be assessed in a 1-year period following the index visit. The study design is shown in Figure 1.

Figure 1. Study design.



Participant Inclusion and Exclusion Criteria

The study will include patients with obesity-associated chronic conditions and with type 2 diabetes who meet the following criteria: patients aged >18 years at their index visit, who are obese (defined as BMI>30 kg/m^2) at their index visit (if BMI>100 kg/m^2, they will be excluded; if there are multiple valid BMI values associated with the index visit, the mean BMI values will be used), with ≥1 diagnosed obesity-associated chronic conditions at any time in any location in their baseline year (see Multimedia Appendix 1 for definition of obesity-associated chronic conditions and qualifying ICD-9-CM and ICD-10-CM diagnosis codes) [25,26], with > 2 ambulatory visits in the baseline year, and with >1 encounter of any type in the follow-up year. Of those, patients with diagnosed type 2 diabetes at any time in any location in their baseline year will be identified.

Outcome Variables

Outcome variables will include overall emergency department visits and overall hospitalizations. These are 2 of the 4 primary outcomes for outpatient continuity of care association with health care use; the effect of geographic, income, ethnic, and racial disparities; and continuity of care protective effects; and are secondary outcomes for characteristics of health care systems with high continuity of care and low utilization. Hospitalizations will include observations visits, and emergency department visits resulting in observation or inpatient visits on the same or following day will be counted as hospitalizations.

Preventable emergency department visits and preventable hospitalizations will be defined by The Agency for Healthcare Research and Quality Prevention Quality Indicators chronic composite measures and will be identified using the primary diagnosis for diabetes short-term complications, diabetes long-term complications, chronic obstructive pulmonary disease or asthma in older adults, hypertension, angina without procedure, uncontrolled diabetes, asthma in younger adults, and lower extremity amputation among patients with diabetes [27]. Hospitalizations will include observations visits. Emergency department visits resulting in observation or inpatient visits on the same or following day will be counted as hospitalizations.

Independent Variables

Continuity of care will be assessed for each patient using a modified version of the Bice-Boxerman index to assess continuity of care at the clinic or facility level [18,19,28]. The continuity of care index is a measure of concentration of the patient-clinic visit patterns ranging from 0 (each visit involved a different practice) to 1 (all visits were made to a single practice). It reflects the relative share of all of a patient's visits during the year that were made to distinct practices. Thus, the higher the index score, the better the modified continuity of care. In this study, a modified Bice-Boxerman continuity of care index score will be used to assess the concentration of the patient-clinic visits patterns during the 12-month baseline period. For this measure, a patient-clinic visit is defined as an encounter with a unique combination of admit date, facility ID (or clinic name), and an ambulatory encounter type. The measure will include both primary and specialty care visits and is calculated as:

[18,19,28]

Low-income status will be assessed at the individual level using patient residence in a low-income area. Patient residence ZIP codes will be linked to the Centers for Medicare & Medicaid Services database of health professional shortage area and low-income ZIP codes to identify patients residing in low-income areas [29].

Residence in health professional shortage area will also be assessed at the individual level using patient residence ZIP code linkage to the Centers for Medicare & Medicaid Services database of health professional shortage area and low-income ZIP codes as described above [29].

A *health system* will be defined to include all ambulatory sites and inpatient facilities included in each respective practice-based research networks. For each health system so defined, the following measures will be calculated using available practice-based research networks and health system data:

Percentage of total providers with primary care specialty (number unique primary care providers / total unique providers), using "ProviderID" and "Provider_Specialty_Primary" labels from practice-based research networks data or, if necessary, using health system provider records.

Percentage of total encounters in ambulatory setting (number of ambulatory encounters / number of ambulatory + hospital encounters) in the practice-based research networks.

Ambulatory site geographic density (number of ambulatory sites per square mile for all unique ZIP codes with one or more health system ambulatory sites or inpatient facilities). We will use the "Facility_Location" label to assess ZIP codes for clinic sites, or if necessary, health system records.

Other covariates such as sociodemographic factors will be assessed at the index visit or the first visit in the baseline year for which data is available and will include age (continuous), gender (male, female), and race (Black or African-American, White, other). Clinical factors will include Charlson comorbidity index [30], and diagnosis of anxiety or depression assessed in the baseline period.

Statistical Analysis

The main analysis will be conducted among patients with obesity-associated chronic conditions. Multivariable negative binomial models will be used to model overall and preventable hospitalizations and emergency department visits. For continuity of care as an outcome, a fractional regression model will be used. Interaction terms between (1) continuity of care and patient residence health professional shortage area designation, (2) continuity of care and patient residence low income status, and (3) continuity of care and patient race will be included to examine whether the association between continuity and health care utilization varies by these factors. The same will be assessed in patients with type 2 diabetes.

Finally, we will conduct a distributed meta-analysis using direct aggregate data from each site following the method employed by Toh [31,32] and Zhou and colleagues [33] to integrate study findings from the 4 different study sites. This approach employs inverse variance-weighted meta-analysis using multivariable confounding adjustment across distributed data networks without sharing of patient-level data [32].

Ethics and Dissemination

This study protocol has been approved by the Institutional Review Board of the 4 sponsoring institutions (University of Tennessee Health Science Center protocol 18-06394-XP, Tulane Medical Center protocol 2018-2306, University of Mississippi Medical Center protocol 2019-0005, Ochsner Health System protocol 2019.035). The findings of this study will be submitted as manuscripts to peer-reviewed journals to aid dissemination to policy makers and other researchers in the field. It will also be presented and discussed at Annual Delta Clinical and Translational Science Health Disparities Conference.

Results

Each site is currently analyzing data, reporting, and submitting the aggregate results; 4 regional health systems across the southern United States have completed collection of data sets and data management at each site. Table 1 shows the characteristics with each health system by demonstrating their geographic characteristics (city, state, and geographic coverage) and hospital characteristics (number of adult hospitals, number of outpatient practices, and number of unique adult patients served). Out of 2,155,860 adult patients served by 53 hospitals and over 400 outpatient practices in the 4 health systems representing Tennessee, Mississippi, Louisiana, and Arkansas, we found that 147,889 patients had obesity-associated chronic conditions and 45,453 patients had type 2 diabetes. Combining results from all sites, data management, and analysis of combined data will be completed by July 2020. Dissemination is expected by the end of 2020.

Table 1. Southern Obesity and Diabetes Coalition practice-based research network locations and characteristics.

Sponsoring institution	City and state	Geographic coverage	Adult hospitals, n	Outpatient practices, n	Unique adult patients served, n
Ochsner Health System	Jefferson, Louisiana	Southeast Louisiana including the Greater New Orleans area, Slidell, Covington, Raceland, and Baton Rouge	40	>100	1,374,751
Tulane Medical Center	New Orleans, Louisiana	Greater New Orleans area	4	34	25,709
University of Mississippi Medical Center	Jackson, Mississippi	Mississippi	4	255	361,288
University of Tennessee Health Science Center	Memphis, Tennessee	West Tennessee, Arkansas, Mississippi	5	60	394,112

Discussion

The 4 health systems and their respective practice-based research networks include patients across 4 southern states, including Arkansas, Louisiana, Mississippi, and Tennessee, with among the highest obesity prevalence in the United States at 37.1%, 36.8%, 39.5% and 34.4%, respectively [1]. Previous studies indicate that health system efforts to increase continuity of primary care for patients with obesity-associated chronic conditions have the potential to improve outcomes and reduce costs [34,35]. There is a critical need to quantify the impact of geographic, income, and racial disparities on continuity of care and health care utilization for people living with obesity-associated chronic conditions and to identify potentially modifiable health system characteristics associated with higher continuity of care and lower health care utilization for these highly vulnerable populations. This study will inform ongoing health system improvement across the southern United States and could lead to major funding for pragmatic research to help communities most affected by disparities to invest in health system transformation to reduce disparities and improve health.

Our research employs an innovative method—inverse variance-weighted meta-analysis across distributed data networks—as employed by the FDA minisentinel program and others [31-33]. The most desirable feature of this approach is that the research process could be easily managed by individual sites and there is no need to share the data with other sites. Each site generates their own outcome results and these outcomes will be synthesized into one treatment effect. As long as each site follows the same research principles and protocol guidelines, this approach will enable our newly established Southern Obesity and Diabetes Coalition and its Cooperative Meta-Analysis Group to immediately support studies across a variety of chronic conditions. Study investigators collaborated to develop standardized protocol to harmonize data collection, management, and analyses across different health systems with differing underlying populations and data sources. This study will assess a very large study cohort with substantial geographic diversity and will provide important information regarding factors impacting health care for patients with obesity-associated chronic conditions. The study will address key knowledge gaps regarding the impact of geographic, income, and racial disparities on continuity of care and major health outcomes for individuals with obesity-associated chronic conditions and with type 2 diabetes.

The study is subject to some limitations. Although we standardized data attributes to the best of our ability, there were still a few variables that were not consistently reported across the sites. As a result, we were unable to assess insurance status, provider-level continuity of care, primary-care continuity of care, and specialty-care continuity of care due to lack of consistent information. The study is also limited by inconsistencies in data collection practices among participating providers. For example, the income and race or ethnicity information were not consistently collected for subset populations across health systems.

This study employs an innovative collaborative research approach and has potential to yield important actionable results that can be employed to improve health care delivery for the vulnerable populations with obesity-associated chronic conditions and with type 2 diabetes. The Southern Obesity and Diabetes Coalition's use of a cooperative meta-analysis method provides a way for researchers to gain the economies of scale needed to answer important pragmatic health services research questions. Furthermore, the worldwide pandemic of obesity and obesity-associated chronic conditions makes this research particularly relevant.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Obesity-associated chronic conditions qualifying diagnosis codes (ICD-9 and ICD-10).
[DOCX File , 35 KB - resprot_v9i9e20788_app1.docx]

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Abbreviations

FDA: Food and Drug Administration
ICD: International Classification of Diseases

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Protocol

Chronic Low-Dose Exposure to Xenoestrogen Ambient Air Pollutants and Breast Cancer Risk: XENAIR Protocol for a Case-Control Study Nested Within the French E3N Cohort

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Abstract

Background: Breast cancer is the most frequent cancer in women in industrialized countries. Lifestyle and environmental factors, particularly endocrine-disrupting pollutants, have been suggested to play a role in breast cancer risk. Current epidemiological studies, although not fully consistent, suggest a positive association of breast cancer risk with exposure to several International Agency for Research on Cancer Group 1 air-pollutant carcinogens, such as particulate matter, polychlorinated biphenyls (PCB), dioxins, Benzo[a]pyrene (BaP), and cadmium. However, epidemiological studies remain scarce and inconsistent. It has been proposed that the menopausal status could modify the relationship between pollutants and breast cancer and that the association varies with hormone receptor status.

Objective: The XENAIR project will investigate the association of breast cancer risk (overall and by hormone receptor status) with chronic exposure to selected air pollutants, including particulate matter, nitrogen dioxide (NO2), ozone (O3), BaP, dioxins, PCB-153, and cadmium.

Methods: Our research is based on a case-control study nested within the French national E3N cohort of 5222 invasive breast cancer cases identified during follow-up from 1990 to 2011, and 5222 matched controls. A questionnaire was sent to all participants to collect their lifetime residential addresses and information on indoor pollution. We will assess these exposures using complementary models of land-use regression, atmospheric dispersion, and regional chemistry-transport (CHIMERE) models, via a Geographic Information System. Associations with breast cancer risk will be modeled using conditional logistic regression models. We will also study the impact of exposure on DNA methylation and interactions with genetic polymorphisms. Appropriate

statistical methods, including Bayesian modeling, principal component analysis, and cluster analysis, will be used to assess the impact of multipollutant exposure. The fraction of breast cancer cases attributable to air pollution will be estimated.

Results: The XENAIR project will contribute to current knowledge on the health effects of air pollution and identify and understand environmental modifiable risk factors related to breast cancer risk.

Conclusions: The results will provide relevant evidence to governments and policy-makers to improve effective public health prevention strategies on air pollution. The XENAIR dataset can be used in future efforts to study the effects of exposure to air pollution associated with other chronic conditions.

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Introduction

Background

Breast cancer is the most common cancer among women worldwide, with an estimated 2.09 million new cancer cases diagnosed globally in 2018 [1]. Over the past 30 years, its incidence has continuously increased in France [1,2]. The rapid increase in the worldwide incidence of breast cancer has been associated with mass screening, menopausal hormonal therapy, and societal changes impacting individuals' lifestyles. Epidemiological studies have suggested an important role of lifestyle and environmental factors, supported by geographical variations of breast cancer incidence and time trends in incidence rates among migrant populations [3-5]. However, a considerable proportion of the risk remains unexplained, and the impact of environmental factors in the etiology of breast cancer has not been fully explored. Epidemiology and laboratory findings suggest that exposure to environmental pollutants, particularly those with estrogenic potential, may influence the development of breast cancer [6,7].

Ambient air pollution is a major public health concern related to a range of adverse health effects, including cancer, and accounting for an estimated 4.2 million deaths per year [8]. In 2013, the International Agency for Research on Cancer (IARC) classified outdoor air pollution as a whole and particulate matter as carcinogenic in humans, principally based on studies of lung and bladder cancers [9]. However, studies on breast cancer are scarce, and results remain inconsistent [10]. A recent meta-analysis of individual data from 15 European cohorts revealed no association between postmenopausal breast cancer and exposure to various classes of particulate matter ($PM_{2.5}$, PM_{10}, and PM coarse); however, they reported a statistically significant positive relationship per 20 $\mu g/m^3$ increase in nitrogen dioxide (NO_2) exposure [11]. Epidemiological evidence suggests an association between breast cancer and NO_2 from traffic-related air pollution [12-15]. Furthermore, women with extremely dense mammography density, a well-established risk factor for breast cancer, were less likely to have higher levels of ozone (O_3) exposure [16]. Breast cancer has also been linked to exposure to endocrine-disrupting pollutants, such as polychlorinated biphenyls (PCBs) [17,18], dioxins [19-21], benzo[a]pyrene (BaP) [12,22], and cadmium [23,24] with sometimes diverging results. Furthermore, studies have reported positive associations between traffic-related BaP exposure as a surrogate for Polycyclic aromatic hydrocarbon (PAH) exposure and breast cancer [25,26]. Cadmium has been classified by IARC as carcinogenic to humans (Group 1), with sufficient evidence for lung cancer [27]. The only study performed on airborne cadmium exposure and breast cancer risk found no evidence of overall increased risk; however, elevated risks for hormone receptor-negative tumors (estrogen receptor and progesterone receptor-negative (ER-PR–)) were observed with higher exposure to cadmium [28].

Indoor pollution is also an important challenge for global health. Around 3 billion people use traditional biomass fuels for household cooking and heating [29], which is a major source of indoor air pollution and exposure to dioxins, PAH, particulate matter, O_3, and NO_2 [30-35]. However, only two studies have investigated the impact of indoor pollution on breast cancer risk [36,37]. Overall, current epidemiological evidence regarding the impact of exposure to ambient air pollution and indoor pollution on breast cancer risk is not fully consistent. In addition, the effects of simultaneous or sequential exposures to multiple compounds have been insufficiently explored, and the evidence supporting the differential effects of menopausal status on breast cancer risk and receptor status is also limited [23]. Breast cancer is no longer considered a homogeneous disease but is a heterogeneous disease composed of several distinct molecular subtypes according to hormone receptor status (ER, PR, and human epidermal growth factor receptor 2, or HER2) [38]. These subtypes each have different prognoses and can affect women differently. Molecular pathological epidemiology, which integrates molecular pathology into epidemiological studies has emerged in order to test for a difference between the association of a specific environmental exposure with subtypes classified by molecular features in determining disease incidence/mortality [39,40].

One of the major limitations of previous studies is the lack of past residential history and/or historical ambient air pollution exposure estimates, which may have resulted in exposure misclassification, contributing to imprecise risk estimates and bias towards the null [41]. Many epidemiological studies have relied on a variety of exposure assessment techniques such as

using data from centrally located ambient air quality monitoring networks, surrogates for exposures. However, such methods are often insufficient for capturing the spatial variability of pollutant concentrations at the local scale, both at the intra-urban scale, and the suburban and rural scale [42]. More complex techniques have been used in recent studies to adequately represent the spatial-temporal variation of pollutants, including land-use regression models, dispersion modeling, chemistry transport models, and hybrid models [43]. These complex methods can be combined to assess exposure to each pollutant at a fine spatial scale and over a large area between 1990 and 2011.

Life-Course Trajectories

Exposures occurring early in life and/or during biological windows of greater sensitivity (ie, in utero and during childhood) have been suggested to be more strongly associated with breast cancer risk [44,45]. However, very few studies have investigated these effects, and the majority of research has been based on adulthood exposures within short observation periods. These studies may have missed critical windows or the cumulative effects of lifetime exposure that could impact breast cancer risk [45,46]. A lack of historical measures makes retrospective exposure reconstruction difficult, especially for earlier periods. Higher breast cancer incidence is commonly observed in large cities compared with rural areas [47]. Also, women born in an urban area are at a greater risk of breast cancer versus women born in rural areas [47]. To our knowledge, no study has investigated the effects of life-course residential trajectories on breast cancer. Residence in an urban area has been suggested to be a surrogate of air pollution exposure released from road traffic, industrial facilities, and waste incineration [48], and to be useful to investigate earlier periods where historical air pollution records are unavailable and back-extrapolation unfeasible [47].

Cumulative and Multiple Exposures

Early evidence suggests that cancer risk may not be a linear function of cumulative carcinogen dose [49]. Individuals are exposed simultaneously to a complex and changing mixture of environmental exposures [50]. These may independently, cumulatively, or interactively influence the risk of developing breast cancer. Furthermore, in single pollutant models, it is unclear whether an observed association is due to the effect of the evaluated pollutant or whether it acts as a surrogate for another pollutant from the same source. Multipollutant approaches need to address the complex structure of mixtures that frequently present multicollinearity. However, such epidemiological studies are limited [51,52].

Gene × Environment Interactions

Current evidence on the role of genetic susceptibility (polymorphisms) related to exposure to ambient air pollution remains limited. Previous epidemiological studies have reported interactions between genetic polymorphisms and some pollutants [53,54]. Saintot et al reported that women carrying the Val CYP1B1 allele and who had lived near a waste incinerator for more than 10 years had a greater risk of breast cancer than those with the Leu/Leu genotype and had never been exposed [55]. A positive association was found in postmenopausal women with a CYP1A1 variant genotype [56].

DNA Methylation

Methylation is one of several epigenetic events involved in the regulation of gene expression, and it can undergo alterations as a consequence of environmental stimuli. Emerging evidence suggests that exposure to ambient air pollutions could influence DNA methylation, producing hypomethylation of repetitive elements in leukocytes and buccal cells, as well as altered methylation at the CpG level in specific genes [57-60]. The biological effects of DNA methylation induced by exposure to air pollution have been investigated in the context of lung cancer risk [61], but little is known about their impact on breast cancer risk.

Objectives

The overall objective of the XENAIR project is to investigate the chronic long-term effects of exposure to multiple ambient air pollutants and risk of breast cancer in a nested case-control study within the ongoing French prospective E3N (Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale) cohort. More specifically, the project aims to assess the associations between chronic exposure to selected ambient air pollutants (particulate matter, NO_2, O_3, BaP, dioxins, PCB 153, and cadmium) estimated from individual residential addresses of study subjects from recruitment (1990) and breast cancer risk. The study will (1) analyze exposure trajectory profiles of individual compounds over time and estimate breast cancer risk associated with each of these exposure profiles; (2) estimate breast cancer risk associated with the weighted cumulative duration of urban residence since birth (used as a surrogate for exposure to ambient air pollutions), as well as indoor exposure from domestic heating and combustion activities; (3) explore approaches to estimate multi-pollutant exposure.

The XENAIR project will further assess potential interactions between long-term exposure to low doses of air pollutants and genetic polymorphisms involved in air pollutant metabolism, to address the hypothesis that breast cancer risk associated with pollutants may depend on individual genetic susceptibility. We will also explore the potential role of DNA methylation as a marker of exposure to ambient air pollutions and as a potential mediator of the effect of ambient air pollutions on breast cancer risk. Additionally, we will estimate the fraction of breast cancers attributable to air pollution in France based on the risk estimates and additional costs of breast cancer management attributable to air pollutants.

Methods

The French E3N Cohort Study

E3N is an ongoing prospective cohort study launched in 1990 to investigate the main risk factors for cancer and severe chronic conditions in women [62]. Participants were recruited between June 1990 and November 1991 among women aged 40-65 years, living in France and insured with the MGEN, a national health insurance plan covering people working with the French education system and their families, and have been biennially

followed-up with self-administered mailed questionnaires. E3N is the French part of the European Prospective Investigation on Cancer (EPIC), a vast European study coordinated by IARC and involving nearly 500,000 Europeans in 10 countries [63]. At recruitment, 98,995 E3N participants filled in a self-administered questionnaire, which included data about lifestyle and reproductive factors, anthropometry, past medical history, and familial history of cancer. To date, twelve questionnaires have been sent to the participants (participation rate at each questionnaire ~80%). Between 1994 and 1998, participants were invited to give a blood specimen. Blood samples were collected from 25,000 women, and saliva samples were later collected from an additional 47,000 women. The occurrence of cancer was self-reported in each questionnaire, and a small number of cancers were further identified from the insurance files or information on causes of death obtained from the National Service on Causes of Deaths. Pathology reports confirming diagnoses of invasive breast cancer (the primary outcome of the present project) were obtained for 93% of self-declared cases, and the proportion of false-positive self-reports was low (<5%). Addresses were recorded at baseline (1990) and the 5- and 9-year follow-up questionnaires (years 1997, 2000, 2002, 2005, 2008, and 2011). Postal codes were recorded at 3- and 4-years follow-up (1993 and 1994). Participants' place of birth (postal code and municipality) was obtained from the first questionnaire and assigned an urban/rural status based on data from the closest national census [64]. Informed consent was obtained from each participant, and the study was approved by the French National Commission for Data Protection and Privacy (CNIL).

Covariate Assessment

Data on established and potential breast cancer risk factors were available from the self-administered questionnaires at baseline. Regular updates have been collected on smoking, anthropometry (height, weight), physical activity, diabetes, hypertension, benign breast disease, gynecological screening, family history of breast cancer (FHbreast cancer), education, and reproductive factors. Women completed two validated self-administered diet history questionnaires (DHQ) in 1993 and 2005. The E3N DHQ covered the daily consumption of 208 food items by collecting food frequencies and portion sizes for eight meals and snacks during the day [65,66]. Dietary exposure to BaP, dioxins, PCB 153, and cadmium will be assessed for each woman by combining consumption data from the E3N DHQ and food contamination data available for France. Contamination data for BaP, dioxins, PCB 153, cadmium are available from the French agency for food safety (ANSES) [67,68].

Study Population

The present study is based on a nested case-control subset of the E3N cohort. It involves 5222 histologically confirmed incident breast cancer cases identified during the 1990-2011 follow-up period. Women were included if they had completed their home address at baseline, lived in the French metropolitan territory during the 1990-2011 follow-up time, and not had any cancer at baseline. For each breast cancer case, one control was randomly selected by incidence density sampling, among cohort participants at risk of breast cancer at the time when the case was diagnosed, using the follow-up time since inclusion into the cohort as the time axis. In order to best select appropriate controls according to the planned studies, two complementary groups of cases were set, according to the presence of a blood sample, saliva sample, or no biological sample available. For the first group of cases (with a blood sample), controls were matched to cases on the department of residence, age (±1 year), date (±3 months), and menopausal status at blood collection. Controls for the second group (without a blood sample) were matched on the same criteria but collected at baseline, and additionally matched on the existence or not of a saliva sample.

Additional Data Collection: Residential History Questionnaire Collection and Assessment of Indoor Air Pollution

A structured questionnaire was sent to all selected cases and controls to collect lifetime residential addresses from date of birth to the present (street address, municipality/city, postal code), school and workplace addresses, commute duration ("less than 30 min," "between 30 and 60 min," "more than 60 min") and type ("walking," "cycling," "motorcycle riding," "driving a diesel car," "driving a gasoline car," or "using public transportation"), and information on domestic heating and combustion activities. We also collected information on the age when starting and stopping living in each reported home. Women were asked to report the period during which their home was built (before 1948, between 1948 and 1974, or after 1974), and whether it overlooked a courtyard or a street (courtyard, street, or both). In terms of indoor heating, they reported their main type of heating (collective central, or individual) and their main source of heating (wood, charcoal, electricity, gas, or fuel). Regarding indoor wood-burning stove or fireplace cooking, women were asked whether they used an indoor wood-burning stove or a fireplace in their home (yes, no), and if yes, the type (stove/wood stove, open fireplace, or closed fireplace). Information on the use and frequency of cooking foods on the barbecue was also collected (never, rarely (once to twice per year)), occasionally, or frequently (at least once a month)). Study participants additionally answered questions on whether they burned green waste (yes, no), and if yes the frequency (never, rarely (once or twice a year, occasionally, or frequently (at least once a month)), and the quantity of green waste burned every year (less than 1 m^3, 1-5 m^3, or more than 5 m^3). The overall response rate was 65.4%.

Geocoding of Residential History and Industrial Sources

The methods of geocoding residential history and industrial sources have been described in detail elsewhere [69]. Briefly, residential histories from the E3N follow-up questionnaires and the residential questionnaire will be geocoded (X and Y coordinates, addresses) using ArcGIS Software (ArcGIS Locator version 10.0, Environmental System Research Institute) and the national addresses database from the National Geographic Institute (BD Adresse, IGN). Geocoding will be performed by a trained technician blinded to the case-control status of the participants.

Air Quality Modeling

Assessment at the national level of exposure to selected pollutants (PM_{10}, $PM_{2.5}$, NO_2, O_3, BaP, dioxins, PCB 153, and cadmium) will be based on complementary models according to data availability and pollutant emissions characteristics (Table 1). Specifically, we will use a regional chemistry-transport model (CHIMERE) [70], an urban gaussian dispersion model (SIRANE) [71], a land-use regression model [72] and a GIS-based metric [73]. A detailed description of these models is provided in Multimedia Appendix 1.

Table 1. Summary of the models used to assess atmospheric exposure.

Type of model (name)	Spatial and temporal resolution	Years	Area	Output/Goal	Pollutants
Eulerian chemistry-transport model (CHIMERE)	7 × 7 km, hourly	1990-2011	National (France)	Concentration/Exposure assessment	NO_2, $PM_{2.5/10}$, O_3, cadmium, dioxins, PCB 153, BaP
National LUR[a] model	50 × 50 m, annually	2010-2012	National (France)	Concentration/Exposure assessment	NO_2, $PM_{2.5/10}$, O_3
Back-extrapolated national LUR model	50 × 50 m, annually	1990-2009	National (France)	Concentration/Exposure assessment	NO_2, $PM_{2.5/10}$, O_3
GIS[b]-based metric	At the subject address, hourly	1990-2011	National (France)	Exposure Metric/Exposure assessment	cadmium, dioxins
Urban dispersion model (SIRANE)	10 × 10 m, hourly	1990, 1995, 2000, 2005, 2010	Local (Lyon)	Concentration/Sensitivity analysis	NO_2, $PM_{2.5/10}$, O_3
Local LUR model	50 × 50 m, annually	2010	Local (Lyon)	Concentration/Sensitivity analysis	NO_2
Back-extrapolated local LUR model	At the subject address, annually	1990, 1995, 2000, 2005,	Local (Lyon)	Concentration/Sensitivity analysis	NO_2

[a]LUR: land-use regression.

[b]GIS: geographic information system.

PM10, PM2.5, NO2, and O3

We will use land-use regression models to estimate PM_{10}, $PM_{2.5}$, NO_2, and O_3 concentrations at the local scale (50 × 50 m) and develop "hybrid" models combining outputs from CHIMERE (concentrations over the whole French territory from 1990 to 2011, with a spatial resolution of 0.125° × 0.0625°) and localized variables describing road traffic and land use, nationwide. A so-called "baseline land-use regression model" will be constructed based on average measurement of 2010-2012 to ensure that meteorological conditions in a particular year do not bias predictions for other years. In this manner, we will also benefit from the largest quantity and the best quality of measurement data. This model will be validated against measurement across France by performing a hold-out validation (ie, independent monitoring sites). Once established, this model will be back-extrapolated until 1990. However, this step will benefit from the CHIMERE modeling results that will provide local concentrations from 2011 to 1990 to help adjust the back-extrapolation.

Dioxins and Cadmium

Ambient air concentration measurements of dioxins and cadmium are extremely fragmented and, therefore, it is difficult to estimate exposures. In addition, these measurements are unevenly distributed over time and space with an increasing number of measurements from the 2000s onwards, while at the same time, emissions are falling sharply, precluding the use of land-use regression models. Since dioxins and cadmium emissions over the period were mainly due to industrial sources and given the size of the study area, the use of dispersion models over the entire territory would not provide a sufficient spatial and temporal resolution to characterize exposure. To estimate dioxins and cadmium exposure at any point in the national territory over the 1990-2011 period, we adopt instead the approach used in a previous epidemiological study, ie, a GIS-based metric [74]. The latter was validated by comparison with a dispersion model in multiple contexts and is based on a detailed emission inventory [73].

BaP and PCB 153

Unlike dioxin and cadmium, no detailed emission inventory is currently available at a local scale for BaP and PCB 153. As a result, background concentrations from CHIMERE will be directly used as the reference concentrations for these compounds. BaP concentrations were already simulated with CHIMERE by Guerreiro et al [75], whereas PCB-153, cadmium, and dioxins are added into the model.

Sensitivity Analysis of Concentration Modeling

A sensitivity analysis will be done to compare the ability of different models to classify subjects correctly according to their exposures. The performance of the models will be compared to each other and with measurement data in ambient air. One of the most important objectives will be to quantify misclassification created by using a national model to assess exposures (see Multimedia Appendix 1).

Statistical Methods and Power Calculation

Associations with breast cancer risk will be modeled using conditional logistic regression models, considering different

concentrations for each compound, and fuel sources for indoor heating and cooking. Exposure variables will be investigated as continuous and categorical variables, and models will be conditioned on the matching factors. All analyses will be adjusted for potential confounding and known breast cancer risk factors available from the self-administered questionnaires. Simple imputation methods will be used for missing continuous data, and a category of missing data will be created for categorical covariates.

Potential effect modification by follow-up time, age, BMI, tobacco smoking status, alcohol consumption, reproductive factors, and birthplace status will be tested using tests for interaction (likelihood ratio test). Further subgroup analyses will be conducted according to tumor hormone receptor status (ER and PR) and menopausal status. Heterogeneity of associations across hormone receptor subgroups will be assessed using polytomous logistic regression models [76].

The potential non-linearity of the relationship between exposures and breast cancer risk will be examined using restricted cubic splines [77] or fractional polynomials. In order to reduce residual confounding, potential non-linearity of the effects of continuous confounders will be accounted for using the same approach [78,79].

B-spline functions will be used in logistic regression models to estimate (1) the relative weight of the exposure dose versus time since recruitment or age at exposure and (2) breast cancer risk associated with the weighted cumulative duration of urban residence since birth (a surrogate for urban air pollutant exposure) [80,81].

To identify exposure trajectory profiles of individual compounds over time since recruitment in the cohort E3N, and to estimate breast cancer risk associated with each of these exposure profiles, we will use joint latent class mixed models [82].

Finally, different approaches will be explored in order to assess multipollutant exposure (Bayesian modeling, principal component analysis) [51,83].

For sensitivity analyses, models will be adjusted for estimated dietary exposure to each pollutant, considering the diet as a route of exposure separate from inhalation.

Table 2 presents different scenarios considered to calculate the statistical power to detect an association between a binary exposure (high versus low level) and the risk of breast cancer, using the power analysis method for matched case-control studies and a 5% type I error [84]. Overall, even for a low exposure prevalence of 20% and a case-control correlation of 0.2, we will have 97% power to detect an odds ratio of 1.2, and 100% power to detect an odds ratio of 1.5.

Table 2. Statistical power and sample size calculation.

Probability of exposure among controls	Correlation of exposure between matched controls and cases	Odds ratio adjusted for the matching variables	Power
0.2	0.5	1.2	0.85
0.2	0.5	1.5	1.00
0.2	0.2	1.2	0.97
0.2	0.2	1.5	1.00
0.5	0.5	1.2	0.96
0.5	0.5	1.5	1.00
0.5	0.2	1.2	0.99
0.5	0.2	1.5	1.00

Gene × Environment Interaction and DNA Methylation Analyses

To explore gene × environment interactions, we will first use a case-only study design, similar to Saintot et al [55], to analyze the interaction of exposure with single nucleotide polymorphisms in the metabolic pathways of dioxins, PCBs, and PAHs (cytochrome P450, glutathione S-transferase, and related pathways), growth factor, and inflammation pathway genes, in 2500 cases from a previous breast cancer study. A second analysis will be done in a nested case-control subset of 2500 cases and 2500 matched controls. DNA methylation analyses will be based on at least 400 case-control pairs with controls matched for age at recruitment, age at diagnosis of the corresponding case, and type of biospecimen (blood or saliva). These methods have been described in Multimedia Appendix 1.

Attributable Fraction and Cost Analyses

The Levin formula will be used to estimate the attributable fraction in the French general population, using our ORs estimates and nationwide exposure estimates [85]. Adopting the French national insurance perspective, direct costs (ie, those associated with diagnosis, surgery, chemotherapy, radiotherapy, and/or hormone therapy, and follow-up +/- relapse) of breast cancer attributable to ambient air pollution exposure will be assessed based on systematic reviews, observational and modeling studies, and expert opinion [86,87]. Costs will be combined with estimated attributable fractions to assess breast cancer treatment costs attributable to air pollutants in France.

Ethics Approval and Consent to Participate

Our research is based on the E3N French national cohort. Informed consent was obtained from all participants, and the

study was approved by the French National Commission for Data Protection and Privacy (CNIL).

Results

The study is still ongoing. XENAIR will provide relevant and innovative evidence to fill gaps regarding the complex association of breast cancer risk with long-term exposure to multiple air pollutants ($PM_{2.5}$, PM_{10}, NO_2, O_3, dioxins, PCB 153, cadmium, and BaP) from 1990 to 2011, using complementary models (land-use regression and atmospheric dispersion models) at a fine spatio-temporal resolution. Our research will contribute to improving our understanding of life-long exposure and exposure at different life stages to urban settings. In addition, the investigation of gene × environment interactions will allow the identification of groups of women with genetic susceptibility to environmental carcinogens, and thus improve our understanding of the interaction of individual susceptibilities with environmental exposure. Furthermore, the identification of methylation markers of exposure to environmental pollutants will contribute to extend our understanding of breast cancer etiology and reveal biomarkers of exposure.

Discussion

This study is prompted by the increasing incidence of breast cancer, although leveling off in recent years, persistent air pollution levels worldwide, and suggestive evidence for an association of breast cancer risk with several ambient air pollutants. To our knowledge, the XENAIR project is one of the largest prospective studies to investigate exposure to ambient air pollution and breast cancer risk, and it should significantly increase current knowledge on the health effects of air pollution. Investigating the impact of environmental exposure on breast cancer risk requires large studies with well-defined exposure information, as well as individuals' risk factors and potential confounders.

Our research is based on the existing French national cohort, E3N [62]. This prospective cohort study is particularly well documented, with updated information every 2 years on established breast cancer risk factors and past medical history. The availability of detailed information on lifestyle factors, family history of breast cancer, and reproductive factors will allow for better control of confounding factors and further investigation of potential effect modifiers. Also, further Molecular pathological epidemiology analyses will be conducted according to hormone receptor status (ER and PR) of breast cancer. Detailed classification of tumor subtypes and their analyses will allow phenotype refinement, improve the identification of specific air pollution risk factors, and characterize the pathogenic molecular mechanisms of breast cancer. The Molecular pathological epidemiology research paradigm provides novel insights into interactions among environment, tumor, and host but also provides an exemplary model of integrative scientific approaches and contributes to advancements in precision medicine, therapy, and prevention [40].

Furthermore, because women from the E3N cohort are mostly teachers or have affiliated occupations, with potentially negligible occupational exposure, bias related to occupational exposures to the selected pollutants will be avoided. Since exposure to dioxins, cadmium, PCB 153, and BaP in the general population occurs through the ingestion of contaminated food and inhalation, the availability of consumption data from the E3N dietary questionnaires available for these compounds will allow further adjustment for dietary exposure [88]. Inhalation is the only route of exposure to PM_{10}, $PM_{2.5}$, NO_2, and O_3 in humans that is relevant to health effects; accordingly, we do not expect confounding from dietary exposure to play a role in exposure to these pollutants. The XENAIR project will also benefit from the large dioxin and cadmium sources inventories (1990-2011) [43,89] as well as the previously developed GIS-based metric [73]. By evaluating the transferability of the ESCAPE land-use regression models [90] to predict air pollution concentrations in large areas in France, XENAIR will contribute to the development of these technological advances for the assessment of long term exposure to air pollutants. One of the major strengths of our study is, however, the combination of CHIMERE and measurements to do back-extrapolation rather than measurements alone.

The use of GIS-based methods, combined with national-scale land-use regression and air dispersion models at different spatial and temporal resolutions, will help to better describe environmental pollutant exposure better. The large dataset created by thorough geocoding of subjects' residential history [69] will enable integrative analyses of additional environmental risk factors. Findings from our research will create a basis for refined assessments of the impact of exposure to air pollution on other diseases within the E3N cohort or other national cohort studies.

Limitations of the XENAIR project include the lack of available historical exposure data before 1990, making it impossible to have a complete individual lifetime dose estimate for the E3N women; however, investigating lifetime urban/rural status will partially remediate this limitation. The spatial resolution of the PCB153 and BaP model will be limited to 7 km^2, which may not be sufficient to describe airborne exposure in dense urban contexts. From a more global perspective, the assessment of historical airborne pollutant exposure will create more uncertainties that must be taken into account. We may minimize the impact of these biases by using different approaches to exposure assessment.

In conclusion, XENAIR will create a large-scale, national dataset on multiple ambient air pollutant exposures and contribute to a better understanding of environmental modifiable risk factors related to breast cancer. The results of our interdisciplinary research will contribute to the concept of the exposome [50] at the individual and societal levels, and provide support to governments and policy-makers to better design effective public health prevention strategies and to promote urban policies in order to reduce exposure to ambient air pollution further. The XENAIR dataset will enable future investigations of the effects of exposure to air pollution associated with other diseases.

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Authors' Contributions

Conception and study design: BF, JG, and GS. Project management: AA, TC, DP, EL, and XM. Supervision: BF, JG, and GS. Exposures assessment/air pollution modeling and geocoding: TC, EF, PS, FC, BB, JC, JG, and XM. Statistical analyses: AA, DP, KL, EL, and AMND.
AA, TC, and BF drafted the first version of the manuscript. All authors have contributed to writing the manuscript or revising it critically. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Detailed description of the different models used for the pollutants exposure assessment.
[DOC File , 507 KB - resprot_v9i9e15167_app1.doc]

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Abbreviations

ANSES: French agency of food safety
BaP: Benzo[a]pyrene
CNIL: commission for data protection and privacy
DHQ: diet history questionnaires
ER: estrogen receptor
E3N: Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale
EPIC: European Prospective Investigation into Cancer and Nutrition
GIS: geographic information system
GWAS: genome-wide association study
IARC: International Agency for Research on Cancer
IGN: National Geographic Institute
LMA: Lyon metropolitan area
LUR: land-use regression
MHT: menopausal hormone therapy
PAH: polycyclic aromatic hydrocarbon
PCBs: polychlorinated biphenyls
PR: progesterone receptor

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Original Paper

Optimizing Antibiotic Prescribing for Acute Respiratory Tract Infection in German Primary Care: Study Protocol for Evaluation of the RESIST Program

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Abstract

Background: The emergence and increased spread of microbial resistance is a major challenge to all health care systems worldwide. In primary care, acute respiratory tract infection (ARTI) is the health condition most strongly related to antibiotic overuse.

Objective: The RESIST program aims at optimizing antibiotic prescribing for ARTI in German primary care. By completing a problem-orientated online training course, physicians are motivated and empowered to utilize patient-centered doctor-patient communication strategies, including shared decision making, in the treatment of patients with ARTI.

Methods: RESIST will be evaluated in the form of a nonrandomized controlled trial. Approximately 3000 physicians of 8 (out of 16) German federal states can participate in the program. Patient and physician data are retrieved from routine health care data. Physicians not participating in the program serve as controls, either among the 8 participating regional Associations of Statutory Health Insurance Physicians (control group 1) or among the remaining associations not participating in RESIST (control group 2). Antibiotic prescription rates before the intervention (T0: 2016, 1st and 2nd quarters of 2017) and after the intervention (T1: 3rd quarter of 2017 until 1st quarter of 2019) will be compared. The primary outcome measure is the overall antibiotic prescription rate for all patients insured with German statutory health insurance before and after provision of the online course. The secondary outcome is the antibiotic prescription rate for coded ARTI before and after the intervention.

Results: RESIST is publicly funded by the Innovations funds of the Federal Joint Committee in Germany and was approved in December 2016. Recruitment of physicians is now completed, and a total of 2460 physicians participated in the intervention. Data analysis started in February 2020.

Conclusions: With approximately 3000 physicians participating in the program, RESIST is among the largest real-world interventions aiming at reducing inadequate antibiotic prescribing for ARTI in primary care. Long-term follow up of up to 21 months will allow for investigating the sustainability of the intervention.

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KEYWORDS

antibacterial agents; respiratory tract infection; upper respiratory tract infection; lower respiratory tract infection; primary care; primary health care; physician-patient relation; shared decision making; antibiotic resistance

Introduction

Background

Growing microbial resistance is a major challenge of all health care systems worldwide. The overuse and misuse of antibiotics in human and veterinary medicine accelerates this development [1,2]. In primary care, acute respiratory tract infection (ARTI) is the health condition most strongly related to antibiotic overuse [3,4]. This is a striking fact, as most cases of ARTI are caused by viruses and/or are self-limiting [5-7]. Considerable geographical variations in antibiotic prescribing for ARTI exist. In Europe, prescribing rates for ARTI range from below 40% in the Netherlands, Scandinavia, and Germany to up to 60% in the United Kingdom and Ireland, and reach up to almost 80% in southern Europe [8]. Reasons for inadequate prescribing include the physician's overestimation of patient expectations toward antibiotic treatment as well as a deceptive "safety culture" in certain cases [9,10].

A considerable number of interventions to reduce inadequate prescribing for ARTI have been developed and evaluated. Overall, the main intervention strategies applied to date include laboratory and point of care testing (POCT), provider or patient education, computerized clinical decision support, prescribing feedback, delayed prescribing, and communication training. There is now sufficient evidence for the effectiveness of communication skills training and laboratory testing/POCT to reduce antibiotic prescribing for ARTI [11,12]. In addition, there is evidence that the effect of these interventions differs according to the level of antibiotic prescribing for ARTI in a given setting. High-prescribing countries benefit from laboratory testing/POCT, whereas medium- and low-prescribing countries show higher effects for communication training [12].

In parallel to the design and evaluation of interventional approaches, an increasing number of nations and supranational bodies have started initiating programs of antimicrobial stewardship. These usually include public information campaigns, education for health care providers, local surveillance of antibiotic resistance, and the provision of research grants to generate evidence necessary to improve antimicrobial stewardship [13]. Along with these initiatives, the German DART 2020 strategy was developed. Apart from strengthening a One Health approach to antimicrobial stewardship by addressing both human and veterinary medicine, supporting research is a major aim of the initiative. In this context, since 2016, the German *Innovationsfonds* granted several programs and trials addressing antimicrobial stewardship. The RESIST program is one of these programs. Within the program, approximately 3000 physicians of 8 (out of 16) German federal states can participate in online training aiming at patient-centered medical care for patients suffering from ARTI. Nationally and internationally, RESIST is one of the largest scientifically evaluated health intervention programs conducted to date. This protocol describes how the program is being evaluated.

Objectives

RESIST aims at optimizing antibiotic prescribing for ARTI in German primary care. By completing a problem-orientated online training course, physicians are motivated and empowered to utilize patient-centered doctor-patient communication strategies, including shared decision making, in the treatment of patients with ARTI. Additionally, the courses provide current data on microbial resistance development and on rational antibiotic use. Moreover, physicians receive information materials for their patients as well as regional prescribing feedback. Based on this protocol, we are assessing whether the RESIST program reduces the number of antibiotics prescribed and, in the case of antibiotic use, impacts the choice of substance. The primary outcome measure is the antibiotic prescription rate for all patients insured with German statutory health insurance before and after provision of the online course. The secondary outcome is the antibiotic prescription rate for coded ARTI before and after the intervention. In addition, using individual qualitative interviews and focus group discussions, the perspective and perceptions of patients, physicians, and practice staff on the program will be evaluated.

Methods

Study Design

As RESIST is primarily a real-world project aiming to address as many participants as funding allows, it is evaluated in the form of a nonrandomized controlled trial. Patient and physician data are retrieved from routine health care data used by the Central Research Institute of Ambulatory Health Care in Germany (Zi). The Zi continuously analyzes prescription and diagnoses data on behalf of all German regional Associations of Statutory Health Insurance Physicians. The data analyzed include information on diagnosis as coded in practices and prescriptions as collected in pharmacies. Physicians not participating in the program serve as controls, either among the 8 statewide participating Associations of Statutory Health Insurance Physicians (control group 1) or among the federal states not eligible for participation in RESIST (control group 2). Antibiotic prescription rates before the intervention (T0: 2016, 1st and 2nd quarters of 2017) and after the intervention (T1: 3rd quarter of 2017 until 1st quarter of 2019) are compared.

Recruitment

Recruitment of participating physicians is undertaken in 8 German federal states and regions (Bavaria, Baden-Wuerttemberg, Lower Saxony, North Rhine, Westphalia-Lippe, Brandenburg, Mecklenburg-Western Pomerania, and Saarland), assisted by the respective regional Association of Statutory Health Insurance Physicians. General practitioners, primary care pediatricians, and practice-based otorhinolaryngologists can enroll in the RESIST program on a

voluntary "first-come, first-served" basis. The maximum number of participating physicians per region is related to the size of the regional association. In total, we aim to include up to 3000 physicians in the program.

Participants

Physicians successfully completing the RESIST online training course are compared to nonparticipating physicians.

Blinding

Participating physicians are not blinded as they enroll voluntarily in the RESIST program.

Intervention

The intervention is based on an online training course consisting of three modules. Each module can be completed within approximately 1 hour. Module 1 focuses on patient-centered doctor-patient communication, and points to typical communicative situations when treating patients with ARTI. Within the module, physicians are encouraged to reflect upon these situations and to question perceived pressure to prescribe antibiotics. Modules 2 and 3 deal with rational antibiotic use in the case of upper and lower respiratory tract infections. After passing the Continued Medical Education–accredited course, physicians receive posters and brochures on rational antibiotic use to display them in their practices or to use them during consultations. Physicians successfully completing the course receive a one-time allowance. In addition, physicians receive further reimbursement for up to 20 patients with ARTI per quarter, which they document as treated according to the strategies adopted after participating in the online training. In addition, participating physicians receive a feedback report on aggregated data on regional antibiotic prescribing patterns. Figures are compared between intervention and control groups. See Multimedia Appendix 1 for more details on each component and module of the intervention [14].

Control Group

Physicians not participating in the program serve as controls, either among the 8 participating regional Associations of Statutory Health Insurance Physicians (control group 1) or among the remaining associations not participating in RESIST (control group 2).

Outcomes

The primary outcome measure is the overall antibiotic prescription rate of all patients insured with a German statutory health insurance before and after the provision of online courses. Secondary outcomes are (a) the antibiotic prescription rate for ARTI in patients aged ≥ 1 year before and after the intervention; (b) the antibiotic prescription rate based on different types of ARTI (eg, otitis media, bronchitis, pneumonia; see Table 1) before and after the intervention in patients aged ≥ 1 year; and (c) quality of antibiotic prescribing for ARTI measured by internationally accredited quality indicators of the European Surveillance of Antimicrobial Consumption Project (ESAC) [15], again before and after the intervention.

Table 1. International Classification of Diseases codes relevant for diagnosing acute respiratory tract infection.

Code	Diagnosis
J00	Acute nasopharyngitis (common cold)
J01	Acute sinusitis
J02	Acute pharyngitis
J03	Acute tonsillitis
J04	Acute laryngitis and tracheitis
J06	Acute upper respiratory infections of multiple and unspecified site
J09	Influenza due to identified zoonotic or pandemic influenza virus
J10	Influenza due to identified seasonal influenza virus
J11	Influenza, virus not identified
J12	Viral pneumonia, not elsewhere classified
J13	Pneumonia due to *Streptococcus pneumoniae*
J14	Pneumonia due to *Haemophilus influenzae*
J15	Bacterial pneumonia, not elsewhere classified
J16	Pneumonia due to other infectious organisms, not elsewhere classified
J17	Pneumonia in diseases classified elsewhere
J18	Pneumonia, organism unspecified
J20	Acute bronchitis
J21	Acute bronchiolitis
J22	Unspecified acute lower respiratory infection
J40	Bronchitis, not specified as acute or chronic
H65	Nonsuppurative otitis media
H66	Suppurative and unspecified otitis media

Sample Size

With respect to the primary outcome, a reduction of the physicians' overall antibiotic prescription rate by 1% is assumed for RESIST (from 33.8% in the control group 1 to 32.8% in the intervention group). Without consideration of cluster effects, 2 × 34,865 patients are needed to show this effect with a power of 80% and a type I error of 5% (two-sided). Assuming an intracluster correlation (ICC) of 8% [16] and an average cluster size of 160 patients per practice, a design effect of 13.72 is determined. Overall, the sample size increases to 2 × 478,400 patients (956,800 patients in total). Thus, 2 × 2990 practices (5980 in total) are needed for the evaluation.

For the secondary outcome, a reduction of 3% in the physicians' antibiotic prescription rate for ARTI is expected (from 30.5% in the control group 1 to 27.5% in the intervention group). Assuming a power of 80% and a type I error of 5% (two-sided), 2 × 3590 patients are required. With an ICC of 8% [16] and an average cluster size of 127 patients (diagnosed with ARTI) per practice, the sample size increases to 2 × 39,751 patients (79,502 patients in total). Hence, 2 × 313 practices are needed (626 practices in total). The sample size necessary to investigate the effect of the intervention on the primary outcome will be adequate to investigate its effect on the secondary outcome as well.

Data Collection, Completeness, and Quality

The trial is based on pseudonymized routine data provided by the Zi. The dataset is based on aggregated practice data. Information collected includes: age groups and sex of patients, ARTI diagnoses (grouped and individual diagnoses), antibiotic prescriptions, group affiliation of the physician (intervention vs control), region, level of urbanization, and type of medical insurance of the patient.

Statistical Methods

Data analyses will be performed in accordance with the STROBE statement [17]. For descriptive statistics, we will report the primary and the secondary outcome for the whole sample and by treatment allocation. Sampling units are practices. This evaluation is designed to confirm the two-sided primary hypothesis that the physicians' antibiotic prescription rate after T1, regardless of the diagnosis, is lower in the intervention group than in control group 1. For investigating the primary outcome, we will use a negative binomial regression with the absolute number of annual antibiotic prescriptions as the dependent variable, the number of patients as the offset variable, and the antibiotic prescription rate before the introduction of RESIST as a covariate. To avoid bias, we will include region, specialization of the physician, proportion of male patients, proportion of different age classes (≤7 years, 8 to 18 years, 19 to 65 years, >66 years), proportion of insurance status (member,

pensioner, noncontributory dependents), and the interaction between the proportion of male patients and region as additional covariates. The comparison between the intervention group and control group 1 is considered in a confirmatory manner. The comparison between the intervention group and control group 2 is additionally examined as a sensitivity analysis. The model for the secondary outcomes will be formulated in the same manner. The results will be represented as incident rate ratios with their 95% CIs and *P* values. Statistical analyses will be carried out with SAS, version 9.4 or the newer version (SAS Institute, Cary, NC, USA).

With respect to quality indicators (according to ESAC), sampling units are practices. The analysis will be carried out in the same way as the analysis of the primary and secondary outcomes considering the requirements of each indicator.

Process Evaluation

Qualitative interviews and focus group discussions will be used to investigate the perspective and perceptions of patients, physicians, and practice staff on the program. First and foremost, the qualitative evaluation focuses on factors fostering or hindering the implementation of the program. To this end, one to two focus group discussions per participating federal state or region will be conducted. Focus group discussions will include 6 to 8 physicians or practice staff members and are assumed to last about 60 to 90 minutes each.

To explore the patients' perspectives, we will additionally conduct up to 50 narrative interviews by telephone. We will interview patients treated for ARTI by physicians participating in the RESIST program. We assume that phone calls will last about 10 to 30 minutes each.

Both focus group discussions and qualitative interviews will be recorded, transcribed verbatim, and analyzed based on content analysis [18].

To verify the findings of this qualitative process evaluation at large, a questionnaire for physicians and for patients suffering from ARTI will be developed. We aim to survey about 1000 individuals in each group. Physicians will be approached directly and will be rewarded monetarily for their support. Patient questionnaires will be distributed via participating physicians.

Harms

The careful and sustainable prescription of antibiotics for ARTI is based on national and international clinical guidelines. Beyond that, the decision to prescribe antibiotics in the individual case remains the choice of the physician. Thus, harms are not expected.

Study Registration

The program was retrospectively registered on December 6, 2018 at the ISRCTN Registry under reference ISRCTN13934505.

Ethical Approval and Consent to Participate

The evaluation was approved by the ethics committee at Rostock University Medical Center in June 2017 (Reference: A 2017-0090). Participating physicians provide written informed consent. However, no informed consent is necessary from the patients, as pseudonymized and de facto anonymized routine data are used based on §80 SGB X.

Availability of Data and Materials

The datasets generated and analyzed during the current study will be available upon request from the Zi (email: zi@zi.de) in the form of aggregated anonymized raw data collected from March 2020 to March 2025. Data will be shared upon request for the purpose of academic research and scientific analyses (such as meta-analysis).

Results

RESIST is publicly funded by the Innovations funds of the Federal Joint Committee (G-BA) in Germany (funding code: 01NVF16005) and was approved in December 2016.

Recruitment of physicians is completed. A total of 2460 physicians participated in the intervention. Data analysis started in February 2020.

Discussion

With up to 3000 physicians participating in the program, RESIST is among the largest real-world interventions aiming at reducing inadequate antibiotic prescribing for ARTI in primary care. Long-term follow up of up to 21 months will allow for investigating the sustainability of the intervention.

As RESIST utilizes an open-label nonrandomized evaluation concept, potential bias has to be carefully addressed. Bias may arise from the fact that physicians most interested in reducing inadequate antibiotic prescriptions are also likely to be those most motivated to take part in RESIST. To counteract this, we make use of an attractive incentivization and reimbursement scheme. In addition, the inclusion of comparable practices not participating in the program (both among participating regions and among those not participating in RESIST) allows for control of this potential source of bias.

We will also minimize bias due to changed coding. For example, a clinically identical patient treated with antibiotics might be coded with lower respiratory tract infection initially but with pneumonia after the intervention, leading to an overestimation of the interventional effect. By measuring the overall antibiotic prescribing rate of antibiotics without regard to any specific disease as the primary outcome measure, we can exclude bias due to coding phenomena.

Last but not least, the RESIST program joins the ranks of other current initiatives to reduce inadequate antibiotic prescribing. Thus, contamination effects between the projects are possible. However, by including a high number of physicians and practices among half of all German states, we believe to be able to address this potential source of bias adequately.

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Authors' Contributions

AA and JI are responsible for the design of the study. CL and AK wrote the manuscript. All authors critically read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Components 1-5 of the intervention.
[DOCX File , 23 KB - resprot_v9i9e18648_app1.docx]

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Abbreviations

ARTI: acute respiratory tract infection
ESAC: European Surveillance of Antimicrobial Consumption Project
ICC: intracluster correlation
POCT: point of care testing
Zi: Central Research Institute of Ambulatory Health Care in German

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Protocol

Remote Assessment of Functional Mobility and Strength in Older Cancer Survivors: Protocol for a Validity and Reliability Study

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Abstract

Background: Older cancer survivors, faced with both age- and treatment-related morbidity, are at increased and premature risk for physical function limitations. Physical performance is an important predictor of disability, quality of life, and premature mortality, and thus is considered an important target of interventions designed to prevent, delay, or attenuate the physical functional decline. Currently, low-cost, valid, and reliable methods to remotely assess physical performance tests that are self-administered by older adults in the home-setting do not exist, thus limiting the reach, scalability, and dissemination of interventions.

Objective: This paper will describe the rationale and design for a study to evaluate the accuracy, reliability, safety, and acceptability of videoconferencing and self-administered tests of functional mobility and strength by older cancer survivors in their own homes.

Methods: To enable remote assessment, participants receive a toolkit and instructions for setting up their test course and communicating with the investigator. Two standard gerontologic performance tests are being evaluated: the Timed Up and Go test and the 30-second chair stand test. Phase 1 of the study evaluates proof-of-concept that older cancer survivors (age ≥60 years) can follow the testing protocol and use a tablet PC to communicate with the study investigator. Phase 2 evaluates the criterion validity of videoconference compared to direct observation of the two physical performance tests. Phase 3 evaluates reliability by enrolling 5-10 participants who agree to repeat the remote assessment (without direct observation). Phase 4 enrolls 5-10 new study participants to complete the remote assessment test protocol. Feedback from participants in each phase is used to refine the test protocol and instructions.

Results: Enrollment began in December 2019. Ten participants completed the Phase 1 proof-of-concept. The study was paused in mid-March 2020 due to the COVID-19 pandemic. The study is expected to be completed by the end of 2020.

Conclusions: This validity and reliability study will provide important information on the acceptability and safety of using videoconferencing to remotely assess two tests of functional mobility and strength, self-administered by older adults in their homes. Videoconferencing has the potential to expand the reach, scalability, and dissemination of interventions to older cancer survivors, and potentially other older adults, especially in rural areas.

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physical function; physical performance; older adults; remote assessment; videoconferencing; cancer survivors; cancer; elderly; physical activity; telehealth

Introduction

Over 16.9 million cancer survivors are living in the United States, and three-quarters are 60 years of age or older [1]. Compared with individuals without a history of cancer, cancer survivors are at increased and premature risk of developing age-related diseases and conditions [2]. It is hypothesized that cancer and its treatment can lead to "a paralleled 'normal' aging trajectory with weakened physiologic reserve (Phase Shift or Accentuated Aging Hypothesis) or an altered aging trajectory with quicker progression to functional decline (Accelerated Aging Hypothesis)" [3]. Older cancer survivors, faced with both age- and treatment-related morbidity, are at increased and premature risk for physical function limitations [4-7]. Compared with the general population, cancer survivors have a two- to five-fold increased risk of having one or more functional limitations [6]. The adverse consequences of functional limitations, especially mobility limitations, include an increased number of falls, hospital/nursing home admissions, diminished quality of life, premature death, and substantial financial costs [8-11]. Thus, interventions have been designed to improve physical functioning or at least attenuate functional decline among older cancer survivors. However, the majority of interventions that collect objective measures of physical functioning require the participant to travel to the research center or clinic for the assessment even when interventions are provided at home. This requirement can result in selection and attrition bias and limits the reach, scalability, and dissemination of interventions.

Unlike self-reported physical function, the collection of objective measures of physical function (ie, physical performance) requires more resources. It has been challenging to collect objective measures of physical function outside of a standardized environment. Common objective measures of physical performance in older adults include the Short Physical Performance Battery, and the Rikli and Jones Senior Fitness Test that assess mobility, strength, balance, agility, endurance, and postural control [12-14]). Traditionally, these objective measures are collected in a clinic or research setting, to standardize both basic test equipment, such as an armless chair of specified height for chair stand tests, and walking courses, which require adequate space that is free of interruptions and fall hazards. Additionally, specialized equipment is more readily available, such as a hand dynamometer for measuring grip strength or motion capture systems for measuring gait and balance. Another advantage of evaluating physical performance in the clinic is the opportunity for trained staff to provide spotting during more advanced tests or for individuals at greater risk of falls or other injuries. However, a major disadvantage of requiring clinic visits is the travel burden experienced by study participants, which may exclude older, rural, or other individuals unable or unwilling to travel for a research study.

One alternative to assessing physical functioning in a standardized setting is to use study staff or community health workers to conduct home visits to collect objective data. However, this can be time-consuming, costly, and difficult to staff, especially if studies include rural-dwelling participants from large geographical areas. Another option is to utilize technology to remotely assess physical performance, that is, collection of physical performance data that does not require travel for either the participant or study staff. For this option to be practical, the technology would need to produce valid and reliable results. Additionally, the technology should be inexpensive, easy for study participants to use, and straightforward for researchers to score and interpret the test results. Moreover, it is critical that such testing be safe.

The past decade has seen tremendous advances in the development and testing of wearable sensors to evaluate important outcomes like physical performance. However, to date, wearable sensors are either very expensive [15-18], proprietary [19,20], require technicians present for testing [15,17,21], and/or involve complex programming code to process the data [22]. For example, commercially available systems that include wearable sensors, such as LEGSys or the Opal, and software to administer and score standard gait tests (eg, Timed Up and Go, or TUG test), provide a range of useful gait parameters [23,24]. However, the cost of each sensor plus the cost to administer and score each performance test is not economical for most physical activity intervention trials.

Smartphone apps with instrumented versions of physical performance tests have been developed and show great promise [22,25-29]. In particular, instrumented versions of the Timed Up and Go test (iTUG) and the 30-second chair stand test (30s-CST), have been developed for either android phones or iPhones. An advantage to this technology is the ability to capture the sub-phases of a test, thus providing information regarding the quality of movement, in addition to providing more accurate quantification of the movement tasks (ie, time in seconds to complete the test or the total number of stands). For example, some apps can distinguish between the sit-to-stand and stand-to-sit subphases of the chair stand test [30], or the sit-to-stand, walk, turn, walk, stand-to-sit subphases of the iTUG test [28-30]. To date, most of these instrumented performance measures are still being evaluated in large studies, such as the PreventIT trial in Europe [30], have been commercialized (and thus are more expensive) [28,29], or are still being refined and evaluated [26,27,31,32].

Furthermore, to our knowledge, only one study has evaluated the self-administration of the instrumented tests by study

participants in the home setting [26]. As noted by Bergquist and colleagues, different usability problems arise when moving the evaluation of an instrumented performance test from the lab to a home-setting [26]. If the apps are intended for unsupervised use in the home setting, then the validity, reliability, usability, and acceptability should be evaluated in that same setting. Thus, further studies are needed before these apps are ready and available for widespread use.

Before COVID-19, telerehabilitation studies have been conducted using videoconferencing to assess physical performance; however, these studies have included a technician or study investigator in the same room or (hospital) building as the study participant during the tests [33-36]. Additionally, few if any of these studies have been tested in rural areas, which often have less reliable high-speed internet necessary for quality video transmission. Similarly, home-based rehabilitation interventions delivered via technology typically have involved an in-person assessment of physical performance, either through home visits by a member of the study team [37,38] or by requiring participants to travel to the research center for data collection [39,40].

At the time our study was designed (pre–COVID-19), low-cost, valid, and reliable methods to remotely assess physical performance tests that are self-administered by older adults in the home setting were not readily available to researchers. Therefore, we propose to use an existing, low-cost, and easy to use technology (videoconferencing) to remotely assess tests of functional mobility and strength that are self-administered by older (≥60 years) cancer survivors. The primary objective of this study is to evaluate the validity, reliability, acceptability, and, most importantly, the safety of having the participants perform two standard gerontologic physical performance tests in their own homes with remote assessment via videoconferencing. These results will be compared to the traditional direct observation (ie, in-person observation and scoring of tests) and accelerometer data. We hypothesize that older cancer survivors, in the presence of a family member or friend, will complete the physical performance self-assessment in the home environment. We further hypothesize that the agreement between the videoconferencing method and the traditional direct observation approach will be within a clinically acceptable limit. The purpose of this paper is to present the research protocol for the validity and reliability study.

Methods

Overall Study Design

The ultimate goal of this research study is to develop a test protocol to allow older cancer survivors to self-administer two tests of functional mobility and strength in their own homes. At the same time, an investigator remotely assesses the tests via videoconferencing. This objective is being achieved over a series of phases. Phase 1 (Proof-of-Concept) will evaluate proof-of-concept that older cancer survivors can follow the testing protocol and use a tablet PC to communicate with a remote assessor. Phase 2 (Measurement Validity) will evaluate the validity of videoconference assessment vs direct observation of physical performance tests. Phase 3 (Reliability) will evaluate the reliability by enrolling a sample of participants from earlier phases to repeat the assessment. Participant feedback from each phase will be used to revise the test protocol and instructions. Phase 4 (Remote Assessment) will enroll new study participants who will complete the revised test protocol and undergo de novo remote assessment of physical performance (see Figure 1 for an overview; see procedures below for details). The Human Research Review Committee at the University of New Mexico Health Sciences Center approved the study.

Figure 1. Phases of the remote assessment study.

Phase Name / Purpose	Proof-of-Concept	Validation	Reliability	Remote Assessment
Objective(s)	Identify technical and non-technical issues with test toolkit, instructions, & procedures	Evaluate accuracy of remote assessment vs. direct observation (time, # chair stands)	Evaluate whether previous participants can repeat assessment	Evaluate whether new participants can complete assessment
Investigator(s)	Direct observer (home visit) Remote assessor	Direct observer (home visit) Remote assessor	Remote Assessor	Remote Assessor
Number of participants	10-12	10-20	5-10	5-10
Timeframe	2-3 months	2-3 months	2 months	2 months

Setting

All testing takes place inside the study participants' homes, in a room and or hallway with adequate space to safely perform the two tests of functional mobility and strength. For Phases 1 and 2, one or more investigators are in the home, directly observing and timing the tests for comparison with the remote assessor. For all phases, an investigator serving as the remote assessor is located offsite.

Participants

Convenience sampling is used to recruit participants for this validity and reliability study. Study flyers are being distributed in areas frequented by older adults, such as primary care clinics, libraries, senior and community centers, and cancer support groups. Additionally, individuals from previously completed studies providing permission for future contact are mailed a letter explaining the new study and inviting them to participate. Individuals expressing interest in the study are assessed for eligibility during a screening telephone call.

Eligibility criteria for the current study are primarily based on criteria to be used in future physical activity interventions aimed at improving physical functioning in older cancer survivors. The criteria include (1) men and women aged 60 years and older, residing in New Mexico; (2) previous diagnosis of cancer (any site, any stage); 3) ≥2 physical function limitations (≥2 functions limited a lot or limited a little on the SF36 Physical Function Subscale, which includes 10-items ranging from self-care to vigorous-intensity activities) [41,42]; (4) able to speak, read, and understand English; (5) participating in less than 120 minutes per week of moderate-to-vigorous physical activity, ie, not meeting physical activity guidelines and accounting for potential over-estimation due to self-report bias. A modified version of the Godin Leisure-Time Exercise Questionnaire that also includes duration is used. Frequency is multiplied by duration for each reported moderate- and strenuous-intensity activity and summed to determine the weekly amount of minutes; (6) living independently and capable of walking three blocks (approximately 1/4 mile or 1300 steps) without stopping to rest; (7) no severe impairments or pre-existing medical limitations for engaging in daily light physical activity (eg, severe orthopedic conditions, dementia, chronic vertigo); (8) no severe hearing, cognitive, or vision deficits that would inhibit communication with the research team via videoconferencing and tablet use; (9) willing to use a tablet computer and videoconferencing software to communicate with a study team member during the assessment; (10) adequate space (minimum of 13 feet by 3 feet) to safely conduct the physical performance tests; (11) availability of a family member or friend to be present (for safety) during remote assessment of performance tests (Phases 3 and 4 only; for Phases 1 and 2, a study team member serves as a safety check when a friend or family member cannot be present during the assessment); and (12) not at high risk for falls (determined using a subset of questions from the Falls Efficacy Scale–International). Individuals who are at high risk for falls and ineligible are asked if they would like more information on Fall Prevention and if yes, they are mailed a brochure from the CDC STEADI Program [43].

Written informed consent for those interested and study eligible is obtained via mail or through REDCap eConsent. Upon receipt of written informed consent, participants are scheduled for the home visit and remote assessment (Phases 1 and 2) or delivery of the test toolkit and subsequent remote assessment (Phases 3 and 4). Prior to the assessment, participants are mailed a location and materials checklist and a 10-foot tape measure. The checklist includes recommendations for choosing a location in their home to safely conduct the tests of functional mobility and strength (Multimedia Appendix 1).

Protocol for the Remote Assessment of Functional Mobility and Strength

Functional Tests

The tests include the TUG test and the 30s-CST. Both of these tests are included in the CDC Stopping Elderly Accidents, Deaths, and Injuries (STEADI) toolkit for assessment of falls [43,44]. These two performance tests incorporate movements typically undertaken during normal daily activities (standing from a chair, walking a short distance, sitting on a chair), and thus represent tasks that are more likely to be safely performed in a clinically unsupervised setting. Both the 30s-CST and TUG tests have been routinely conducted in adult populations with functional limitations such as cerebral palsy, Chronic obstructive pulmonary disease, knee osteoarthritis, low back pain, multiple sclerosis, Parkinson's disease, renal transplant, rheumatoid arthritis, stroke, vestibular disorders, and frail elderly [45,46].

The TUG test is measured as the time to stand from a standard chair, walk 10 feet, turn around (180° turn), return to the chair, and sit down [44,47]. The TUG test is a measure of mobility and balance and has good validity ($0.6<r<0.85$) [47,48], and excellent reliability (intraclass coefficient, ICC>0.95) [47,49,50]. This timed test is to be performed as quickly and safely as possible. The 30s-CST involves standing up from a chair and sitting down as quickly and safely as possible, preferably without the use of upper extremity support [44,51]. It is measured by the number of times a person comes to a full standing position from a chair in 30 seconds. The 30s-CST is a measure of lower extremity strength and dynamic balance and has good validity ($0.7<r<0.8$) and excellent reliability (ICC 0.84-0.92) [51]. Both tests are timed with a stopwatch.

Test Tool Kit

The test kit includes an Android tablet, a Wi-Fi hotspot, a tablet stand, an activity monitor, and a measurement tool with a pop-up cone to mark 10 feet for the TUG test (Figures 2 and 3). A written instruction booklet includes information on how to set up the tablet and wireless internet hotspot, attach the activity monitor, set up their test area, accept the videoconference call, and repack the toolkit. Participants are also asked to watch a video on their tablet, which demonstrates the performance tests, safety measures, and instructions for setting up their test area. Further instructions are provided by the investigator (remote assessor) via videoconferencing before conducting the assessment.

Figure 2. Toolkit for the remote assessment of functional mobility and strength among older cancer survivors.

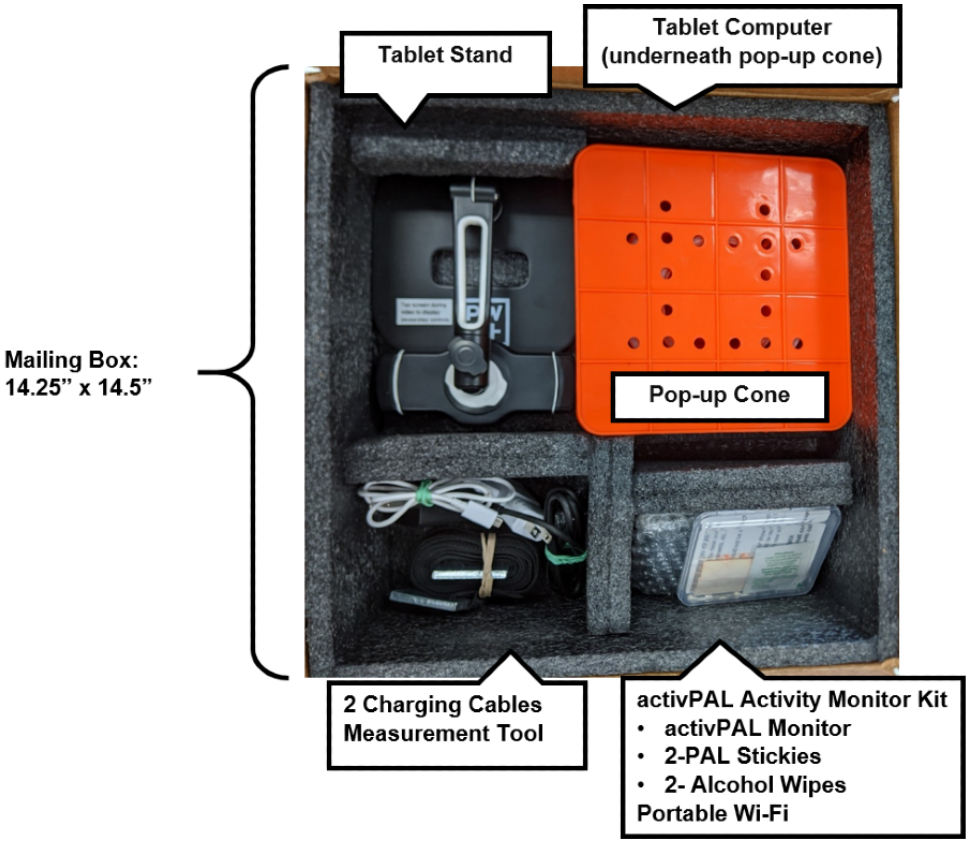

Figure 3. Toolkit for the remote assessment of functional mobility and strength among older cancer survivors (left to right: orange pop-up cone with black 10-foot measurement tool; tablet in tablet stand; Wi-Fi mobile hotspot; instruction booklet; activPAL activity monitor kit with alcohol wipes and adhesives).

Due to the potential for video lag or stutter during the videoconferencing call, participants wear an activity monitor during their physical performance tests. The activPAL3 is a small, light-weight research-grade monitor (2.4 × 4.3 × 0.5 cm; 10 g) worn on the thigh (PAL Technologies, Glasgow). The device includes both an inclinometer (to detect a change in position) and a triaxial accelerometer (to measure acceleration). The activPAL3 provides accurate measures of sitting (or lying), standing, and stepping [52-55]. The time-stamped data (sitting, standing, and stepping) is used to assess the measurement validity of the videoconferencing method to assess physical performance. Both written and video instructions are included to instruct study participants on how to attach the ActivPAL3 monitor. The monitor is attached to the anterior midline of the

thigh (dominant leg) using a PALSticki (a double-sided hypoallergenic sticky pad).

Videoconferencing and Recording Software

Skype was selected as the video conferencing software due to the low-cost (free version), ease of use, and potential for familiarity among the study population. Videos are recorded and saved for quality control and to allow intra- and interrater reliability testing. During the proof-of-concept phase, it was discovered that the stored videos were cropped, reducing the field of view of the test area. Therefore, the software to record and store the videos was changed to SnagIT, a low-cost screen capture and recording software.

The remote assessor, located on campus using a reliable wireless internet connection, initiates the Skype call with the study participant. During the call, the remote assessor reviews the safety checklist with the participant and verifies the testing space is adequate and safe for conducting the two tests of functional mobility and strength. The remote assessor reviews the instructions for the tests, answers any questions, verifies activity monitor application, and tells the participant when to start/stop each test.

Procedures: Study Phases

The study objective is achieved over a series of phases (Figure 1). We are applying a similar concept of "saturation" as is done in qualitative studies. In qualitative studies, the number of focus groups or interviews is based on the saturation point, that is, the point at which no new information is learned. For the current study, we include a range for the number of participants to be included in each study phase. At the point at which no new information is learned, ie, no further adjustments are needed to the test protocol, and we proceed to the next phase.

Phase 1: Proof-of-Concept

The first phase is a proof-of-concept that participants can follow the testing protocol and use the tablet PC to communicate with the investigator. The investigator tracks technology issues (use of a tablet, cellular reception, audio, and video quality) and nontechnology issues (understanding of test instructions, safety issues) during the home visits (direct observer). The investigator observes the participant unpacking the toolkit, reviewing the written and video instructions, applying the activity monitor, setting up the test course, communicating with the remote assessor, performing the gerontologic tests, and repacking the toolkit. Once the assessment is complete, the participant is debriefed by the direct observer. The debriefing opens with broad questioning that captures a participant's general comments on how the assessment could be improved, and then specifically addresses any concerns regarding safety, the clarity of both written and verbal instructions, and comments about the toolkit (contents, packaging). The test protocol and instructions are refined based on what is learned during the proof-of-concept phase (10-12 participants).

Phase 2: Measurement Validity

Next, 10-20 new participants are enrolled to evaluate the criterion validity of measuring physical performance via videoconference compared to the existing gold standard, direct observation (in-person observation and scoring of the tests). We are testing whether the remote assessment via videoconferencing produces similar measurements (ie, test scores) as the traditional (direct observation) method. While one investigator is in a private office on campus with excellent Wi-Fi service conducting the videoconference assessment (remote assessor), another investigator is in the participant's home to directly observe and evaluate the barriers and impediments related to the technology and test protocol (direct observer). The performance tests are assessed simultaneously by the two investigators to eliminate intraparticipant variation that would occur with sequential assessments. A simultaneous assessment (direct observation and remote) vs sequential assessments avoids learning effects (among high performers) and fatigability (among low performers). The remote assessor communicates with the participant during the assessment, provides instructions, and starts, stops, and times each test using a standard stopwatch. The direct observer times each test based on the remote assessor's cues. Communication occurs between the remote assessor and the participant. The direct observer does not communicate directly with the participant, unless there is a safety issue (eg, pet walking through the test course, creating a tripping hazard), until the end of the assessment. At the end of the assessment, the participant provides feedback, which is used to improve the test instructions or protocol (as described in Phase 1). After completing assessments with 10 participants without a major change in the test protocol, we will proceed to the next phase.

Phase 3: Reliability

This phase involves participants repeating the test protocol, but without an investigator in their home during the assessment (ie, no direct observation). This phase tests the ability of the participant to receive the box of test instructions and materials in the mail, unpack the box, set up their test area, communicate with the remote assessor via videoconferencing, pack up the box, and return it (postage paid) to the study team. By eliminating the home visit with the direct observer, participants will have more time to review the test instructions, set up their test course, and will be restricted to communication with the remote assessor. This step involves 5-10 participants from Phases 1 and 2, who provide approval for future contact and express interest in repeating the assessment. Since these participants will have already completed the study, we anticipate the test instructions should be sufficient for the participants to safely self-administer the two physical performance tests in their own home, while communicating with the remote assessor via videoconferencing. Otherwise, further improvements/clarifications to the test instructions will be made. Once five participants have successfully and safely completed the test protocol, we will proceed to Phase 4.

Phase 4: Remote Assessment

This phase is the same as Phase 3, except it includes newly enrolled participants who will complete the revised test protocol and undergo de novo remote assessment of physical performance to eliminate the practice effect that is likely to occur in Phase 3. The enrollment goal for this phase is 5-10 participants. The goal of this phase is to have a finalized test protocol, toolkit,

and instructions that older cancer survivors find acceptable to self-administer and safely perform the two tests of functional mobility and strength in their homes.

For safety purposes, a friend, neighbor, or relative is requested to be present during the assessment. This person can communicate via the videoconferencing session with the investigator and must have access to a telephone should medical attention be required. As needed, this person may assist the study participant with reading/understanding the instructions and setting up the test course. If this person is unable to be present during the assessment once it has been scheduled, then the research investigator conducting the direct observation covers their responsibilities (Phases 1 and 2). Otherwise, the assessment is rescheduled (Phases 3 and 4).

The anticipated number of enrolled participants ranges from 30 to 52. For each phase of the study, participants receive a $50 gift card for the completed assessment to compensate them for their time and participation.

Subjective Measures

Sociodemographics, health-related characteristics, and medical history are used to characterize the study population. Sociodemographic data collected by the survey include age, sex, race/ethnicity, education, income range, and marital status. Health-related characteristics include smoking status, and self-reported height and weight (used to calculate body mass index (BMI; kg/m^2). Cancer data are obtained via self-report (cancer type, year of diagnosis, and treatment received (yes/no): surgery, chemotherapy, radiation, hormone therapy). The Self-Administered Comorbidity Questionnaire [56,57] is used to assess the number of medical conditions and their impact on usual activities.

The full version of the Falls Efficacy Scale–International is completed by all enrolled participants for comparison with the shortened version used for screening. Respondent choices for concerns about falling while performing each of the sixteen activities include “not at all concerned,” “somewhat concerned,” “fairly concerned,” and “very concerned.” The scores on the full version of the questionnaire ranged from 16 to 64. Prior studies have considered a score of 24 and above as having a high concern of falling [38,58]. Fall risk assessed from the full version of the questionnaire will be used to characterize the study population.

The PROMIS-29 Profile [59] is a combination of short-forms designed to assess patient-reported outcomes across a variety of chronic diseases, including cancer [60-63]. It includes four items from seven domains (anxiety, depression, pain interference, fatigue, sleep disturbance, satisfaction with participation in social roles, and physical function) using a 5-point Likert-type scale; 1 item for pain intensity (an 11-point rating scale). Scores are normed to a general population. These instruments, developed by the NIH, have strong validity, reliability, and are responsive to change [60,62,63]. This quality of life data will also be used to characterize the health and well-being of the study population.

Analyses

Descriptive statistics will be used to describe the sociodemographic characteristics, health-related factors, fall risk, and health-related quality of life of the study population.

We will evaluate the criterion validity of videoconference vs direct observation of the tests of functional mobility and strength. Both performance tests are timed tests (time in seconds to complete the TUG test; number of chair stands in 30 seconds). The validity of the videoconference assessment will be evaluated by estimating the limits of agreement between the two methods [64], ie, the interval containing 95% of the between-measures differences between measurements. The videoconference assessment will be considered valid if the limits of agreement are within a clinically acceptable limit [64]. This limit will be determined *a priori* based on the results from the interrater reliability evaluation using data collected during the proof-of-concept (Phase 1 of the study including the first 10 participants), thus providing a better idea of interrater differences in timing these tests under ideal conditions, ie, both investigators observing the tests from the saved video recording. The clinically acceptable limit will need to take the interrater difference into account, ie, a limit that is at or above the interrater difference under ideal conditions.

Intra- and interrater reliability testing will occur 6-8 weeks after completion of the home visit (Phases 1 and 2). The investigator who performed the videoconferencing assessment will watch the video recording and re-score the tests to determine intrarater reliability. Two different investigators will watch the video recordings and score the tests (using a stopwatch) to determine interrater reliability. All investigators will receive specific training in how to time the performance tests in the same way. We will calculate ICC to examine intrarater and interrater reliability of the videoconference assessments of physical performance. We hope to achieve ICCs that reflect good to excellent reliability (ICC >0.59) [65].

We will also evaluate the validity of videoconference vs accelerometer data collected from the physical performance tests. ActivPAL3 data will be downloaded using the activPAL software (version 8; PAL Technologies Limited). Attempts will be made to synchronize the event files to the video in order to obtain objective measures of the degree to which video assessments might accurately reflect actual motion recorded objectively by other means. The event files include the start and stop time for each sitting, standing, and stepping event, and the duration of each event. The event file (CSV file) will be processed using the activPAL Processing R package (version 1.0.2) [66,67]. Once the sit-to-stand and stand-to-sit transitions have been identified (derived from activPAL’s inclinometer data), we will use similar methods as Pickford et al to use the peak angular velocity of thigh rotation (derived from activPAL’s acceleration data) to accurately determine the start and end of the movements for both the TUG test and the 30-s CST [68].

Results

Enrollment began in December of 2019 and is ongoing. Phase I was completed in February 2020. Proof-of-concept that

participants can follow the testing protocol and use the tablet PC to communicate with the investigator was established with 10 cancer survivors, aged 70.5 (SD 6.5) years. The test protocol was refined based on what was learned in this phase, which primarily comprised enhancements to both the written and video instructions per participant feedback. Ten participants have been enrolled in the Validity Phase (Phase 2); however, only 5 participants completed the assessment before the study was paused due to COVID-19. Preparations are underway to resume the study while taking precautions to keep participants and the study team safe. The study is expected to be completed by the end of 2020.

Discussion

Physical functioning is an important predictor of future disability, loss of independence, and premature mortality. Thus, physical functioning is frequently targeted in interventions for older cancer survivors, especially those with comorbidities or existing functional limitations. To our knowledge, low-cost, valid, reliable, and easy to use methods to remotely assess physical performance in older adults in the home environment are not readily available to the research community. Soon, wearable sensors and smartphone apps will likely meet these criteria. In the meantime, videoconferencing has a role to play in remote assessment, with the added benefits of verification of a safe environment for conducting the physical performance tests, and of successful completion of the tests, including adherence to the test instructions by study participants. The current study is evaluating the validity and reliability of using videoconferencing to remotely assess two tests of functional mobility and strength, self-administered by older cancer survivors in the home setting. While this study was designed to reduce travel burden to a clinical site for assessment with rural participants in mind, the COVID-19 pandemic underscores the need for remote assessment.

Our test protocol provides a complete toolkit and instructions to assist older cancer survivors of varying proficiency with technology, to videoconference with an investigator during the remote assessment. The simplicity of this test protocol is both a limitation and a strength. Our test protocol includes a limited number of performance tests, the TUG, and 30-s CST, which are considered basic, yet standard gerontologic performance tests. This protocol could easily be modified to include other similar tests, such as the 5-times sit to stand test or the 8-foot usual walk [12]. However, more advanced balance tests (eg, tandem stance [12], especially with eyes closed) and endurance tests (eg, two-minute step test [13,69]), would require additional safety measures. Training of the family member/caregiver on how to spot the participant during these tests would also help reduce the risk of falls during more advanced tests; however, this would require careful attention to the age and health status of the individual spotting the participant. We excluded individuals at high fall risk, primarily associated with basic activities performed at home (eg, cleaning the house and walking around in your house), rather than exclusion based on less common and more avoidable activities (eg, walking on a slippery surface or an uneven surface). Individuals at high risk for falls would likely require a more elaborate test protocol, especially for safety measures, including spotting during the tests by a trained family member/caregiver, and a physical therapist or someone with relevant clinical expertise to serve as the remote assessor.

Another limitation is the lack of standardization of the space and equipment used for testing within individual homes. Many homes are not conducive for this type of testing, especially older or smaller homes, which may have smaller rooms, doorways, and walkways, or furniture that is not easily moved. Another issue for mobility tests is having adequate space without transitions between the type of flooring (eg, tile or hardwood to carpet) or level of flooring (eg, sunken living rooms). While an individual's normal daily activities include movements associated with many of the basic performance tests (eg, standing up from a chair, walking a short distance, turning around), the combination of movements at a faster speed (due to timed tests), especially in a crowded space, requires consideration. Videoconferencing allows for a more thorough examination of the test space and other factors affecting safety (eg, pets or children entering the test area during testing), compared to remote assessment via sensors or apps. The goal of our protocol is to strike the right balance between safety and meaningful data collection.

It is important to note that our study design and protocol were created before the COVID-19 pandemic, and thus represent a preliminary evaluation of safety and acceptability of self-administered performance tests by older adults in the home setting. Future directions include the expansion of the current protocol to include the evaluation of additional performance tests. Additionally, we anticipate that soon, low-cost, easy to use, valid and reliable sensors and apps will be available for widespread use by the research community after final evaluation and usability testing in the home environment. The sensors and apps will be able to provide greater detail and more precise measurements of the timed tests, as well as the quality of movement during the different phases of the test. Nevertheless, videoconferencing would still be of value to verify that the test area is acceptable in terms of safety and space, the test equipment has been set up properly, and the participant is wearing appropriate footwear (eg, sturdy walking shoes with nonslip soles). Additionally, videoconferencing would allow verification that the test subject is performing the tests appropriately and safely, and would allow the remote assessor to stop the test early if necessary.

This protocol was developed for use in a nontherapeutic research setting. Nevertheless, our protocol could be easily adapted to allow therapists and healthcare professionals to follow-up with their aging patients in the home setting. The current toolkit includes a tablet computer and portable wireless hotspot, which allows individuals without a portable device containing reliable, high-speed internet to participate in video conferencing. A smaller toolkit could be used for individuals who own and are comfortable using a laptop, tablet, or smartphone for videoconferencing with a health professional. Conversely, additional equipment, such as a hand dynamometer to measure grip strength, could be included in the toolkit. The cost of the contents of the toolkit may warrant insurance, should the toolkit be stolen (eg, porch pirates).

This feasibility study will provide important information on the validity, reliability, acceptability, and safety of using videoconferencing to remotely assess physical performance tests, self-administered by older cancer survivors in the home setting. If feasible and safe, this remote assessment protocol and toolkit will provide a low-cost and easy to use method to collect objective data for an important measure of physical health in older cancer survivors. The TUG and the 30-s CST are standard gerontologic tests that are responsive to change, and thus represent useful tests for interventions aiming to improve physical performance. Remote assessment eliminates travel burden for the participant and is cost-effective. Furthermore, this method will allow future interventions to expand the reach to rural, older cancer survivors, an underserved population.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Checklist provided to older cancer survivors prior to the remote assessment of two tests of functional mobility and strength (Timed Up and Go test, 30-second chair stand test).
[DOCX File , 22 KB - resprot_v9i9e20834_app1.docx]

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Abbreviations

30s-CST: 30-second chair stand test
ICC: intraclass correlation coefficient
STEADI: Stopping Elderly Accidents, Deaths, and Injuries
TUG: timed up and go test

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Protocol

Peer-to-Peer Health Communication in Older Adults' Online Communities: Protocol for a Qualitative Netnographic Study and Co-Design Approach

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Abstract

Background: Online communities provide an environment in which people with similar health concerns can interact and access content that can support the self-management of long-term conditions (LTCs). Recently, the importance of online social networks as sources of health information and social support has been brought into focus with the emergence and widespread societal impacts of COVID-19. Although online communities exist for older adults, little is known about the specific health and self-care topics that older people discuss in such environments and how these relate to users' support needs and outcomes. A better understanding of users' needs and peer-to-peer communication in these communities is necessary to inform the design of information and communication technology (ICT) interventions that are relevant to older people and their peer supporters.

Objective: This study aims to use a two-phase, web-based ethnographic (netnography) and co-design approach to explore specific health care and self-care topics that older adults discuss in a UK-based online community and how peer supporters respond to these queries with informational and/or social support and engage with stakeholders to define the needs and requirements for new ICT-based interventions capable of reducing social isolation and facilitating LTC self-management support.

Methods: The first phase of the research will involve a qualitative netnographic analysis of posts in discussion forums in a publicly accessible online community. The second phase will involve co-design workshops with health care consumers (ie, older adults and carers) and service providers to determine the needs and requirements for new ICT-based interventions and digital innovations. Constructivist grounded theory will be used in the first phase; in the second phase, the co-design workshops will be audiorecorded and analyzed thematically.

Results: This research project is in progress. Permission was obtained from the website administrator to use materials from the social media forum; data collection for the first phase began in April 2020. The second phase of the study is expected to begin in late 2020. This study is due to be completed by the end of 2021.

Conclusions: This study is the first, to the best of our knowledge, to combine qualitative netnography with an iterative co-design framework to specify the needs and requirements for new ICT-based interventions. The findings from this study will inform the next phase of the multiphase knowledge translation project and will provide insights into the potential of online peer health communities to reduce social isolation and facilitate chronic illness self-management support and self-care.

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KEYWORDS

aged; chronic illness and disease; long-term conditions; self-management; peer support; social media; online community; netnography; co-design; COVID-19

Introduction

Background

Social connections are critical to psychological and physical well-being and are an important component of long-term condition (LTC) self-management support [1-5]. However, for many older adults, reduced mobility, declining health, and separation from family members and friends can make it difficult to access their formal and informal care and social support systems [6,7]. Owing to the COVID-19 pandemic, the health risks of prolonged lockdowns (ie, *stay-at-home* or *shelter-in-place* ordinances given by governments or authorities for enforcing social distancing) have come to the fore as older populations are told to self-isolate for self-protection and to mitigate the spread of severe acute respiratory syndrome coronavirus 2 [8]. Among the health risks, social isolation has been identified as a primary public health concern, amplifying the burden of neurocognitive, autoimmune, cardiovascular, and mental health problems, such as anxiety and depression [8,9]. During the current COVID-19 pandemic, social isolation is expected to disproportionately affect older people, particularly those without close friends or family whose main source of social contact is outside the home [8]. In light of this context, information and communication technologies (ICTs) can play a potentially important role in connecting older adults and their carers to health-related content and supportive social networks, irrespective of their geographical location, physical ability, or the accessibility of health care services [10-13].

Although older people can access health information from their primary health care provider, unmet needs are frequently reported in the literature [1,14,15], with many patients seeking supplementary information and support from online sources [16-20]. Online communities are a source of peer-to-peer communication that enables users to access health-related content and to interact with others for information or social support [11,21]. An online community is defined as “a large, collectivity of voluntary members...whose members share a common interest, experience, or conviction and positive regard for other members, and who interact with one another and contribute to the collectivity primarily over the Net” [22]. These services invite users with common interests or experiences to interact with one another and exchange information and support. By participating in online discussion boards or forums, members can access a network of individuals facing similar situations, learn from others’ experiences or coping strategies, and share views on self-care and self-management activities in relation to specific health conditions [23,24]. Most discussion forums in online communities are asynchronous, enabling users to post and respond to messages at any time and have a hierarchical structure, containing several distinct message boards arranged thematically [25]. Each board contains different threads that consist of an initial post through which a member initiates a new discussion by describing an experience, asking a question, or soliciting advice; other members can then contribute by posting replies.

Older people may find that the content generated and shared by members of online communities differs from and is preferable to the health information available on general websites such as WebMD and the websites of government health or nonprofit organizations [23,26,27]. Content generated and shared by members of online communities may be perceived as more credible and relevant to users’ personal experiences or current symptoms, particularly if the web-based content is readily available and the information provided by health care providers and other offline sources is difficult to access or understand [11,21,24,28]. Moreover, members of online communities may find it more acceptable to receive health information and advice from peers having the same diagnosis, symptoms, or health-related decisions [13,29]. The benefits of participating in online communities in terms of supporting health literacy, resilience, empowerment, psychosocial well-being, and LTC self-management have been documented in the research literature [19,23,30-34]. However, to date, relatively little research attention has been given to the specific health care and self-care topics that older adults discuss in online communities and how peer supporters respond to such queries with informational and social support. This limits opportunities to develop novel digital pathways to facilitate social connectedness, self-care, and LTC self-management support amid the social distancing regulations and increased pressure on health care systems arising from the COVID-19 pandemic.

Previous studies of online health communities have focused on psychological, marketing, and health informatics theories to explain key variables in determining patients’ motivations for participating in online communities and how the information exchanged therein is applied in managing their health [21,35-39]. An important finding from this research is that members of online communities reported general benefits of participation, such as better general LTC self-management capabilities, and specific benefits of participation, such as collaborative problem solving, communication skills and strategies, and approaches to managing negative emotions [24]. A meta-synthesis of qualitative research by Allen et al [28] identified 6 main themes in relation to the negotiation of LTC self-management support in online communities. These themes were then synthesized into an argument centered around 4 key mechanisms for online self-management support: (1) collective knowledge and identification through lived experience; (2) support, information, and engagement through readily accessible online relationships; (3) sociability that extends beyond illness;

and (4) online disinhibition as a facilitator in the negotiation of self-management support. From a research perspective, the novelty and significance of this type of web-based research lies in the opportunity to understand and embrace an emerging channel through which individuals act collectively, co-creating understandings and providing peer support outside the remit of traditional health care systems [37]. Such research can also offer a rich source of data on patient-reported outcomes and psychosocial needs [15] that can be collected *naturalistically* (eg, without researcher influence) [40].

Netnography is a web-based ethnographic method for studying cyber cultures "sitting within a broader methodological context of online or virtual ethnography" [41] and a useful exploratory tool for understanding consumer perceptions, experiences, learning, and behaviors in online social networks and communities [42-45]. Netnography studies apply naturalistic, multimethod, and multimodal ethnographic approaches to technologically mediated behaviors and interactions in online social networks [42,43]. Studies of online communities are often less obtrusive, less resource intensive, and more flexible than traditional ethnographic approaches and have been combined with methods such as social network analysis, interviews, and surveys [45,46]. Although studies of online communities have provided insights into consumer cultures and behaviors necessary to inform consumer services, research, and practice [46], few studies have used netnography to research online health communities, specifically for older adults [47-49]. This can partially be explained by the initial presentation of netnography as a marketing research technique [42]. As a result, it has been used predominantly in studying web-based brand communities in connection to older people's leisure and entertainment [50,51].

Within the fields of marketing and consumer behavior, netnography has been used to examine topics such as consumer identity (eg, identity construction), electronic word of mouth (eg, peer influence), consumption experiences (eg, experience creation), co-creation (eg, product development), and various aspects of online community participation (eg, online cultures, consumer learning) [44-46]. Although netnography has numerous promising applications, it has seen limited use in health care research, with earlier studies exploring topics such as eating disorders [52], breastfeeding [53], alcohol-related problems [54], codeine addiction [55], and the relationship between sexuality and well-being in older adulthood [56]. Moreover, although netnography offers several benefits over offline methods, particularly with regard to the ability to collect timely and continuous naturalistic data, the approach is yet to be utilized to explore the needs and concerns that older adults discuss in online communities in relation to LTC self-management and self-care as a starting point for health research co-design.

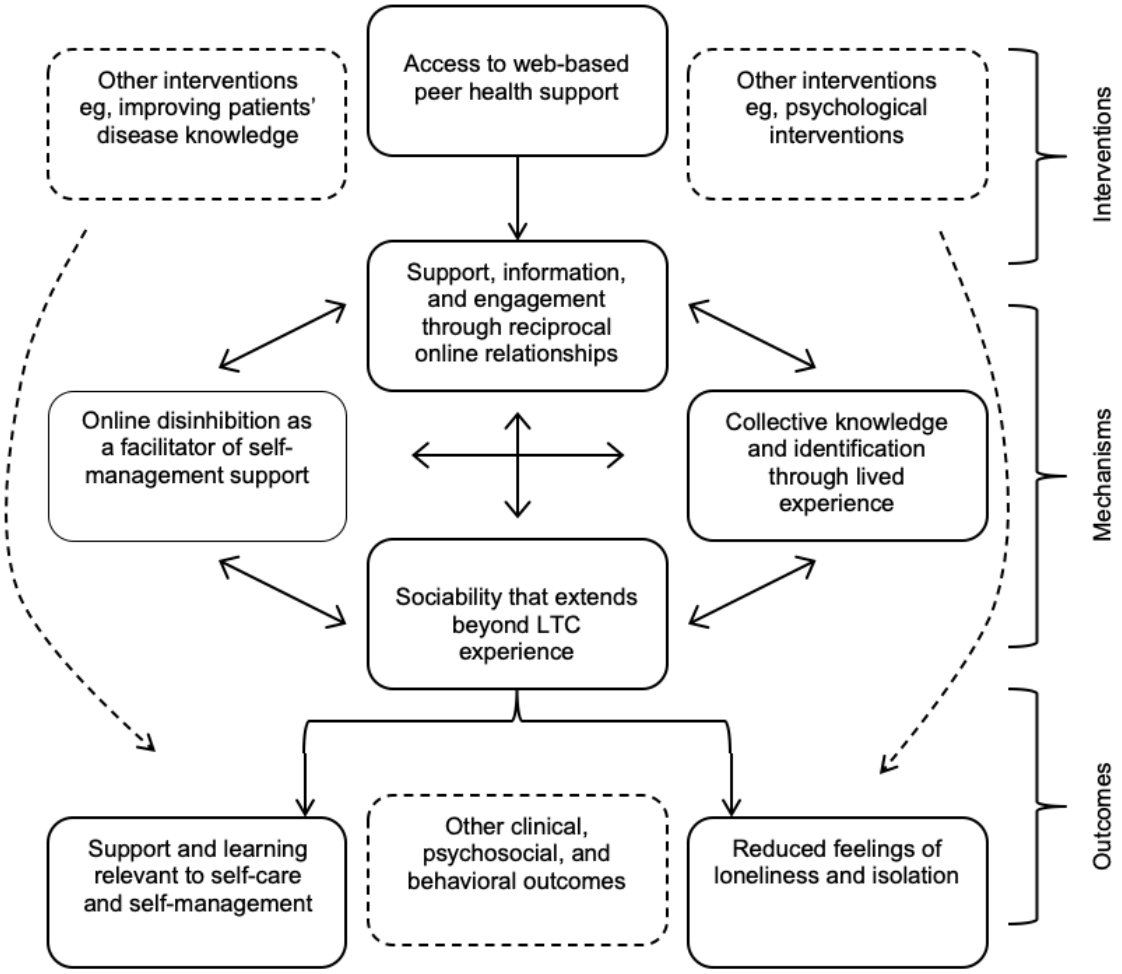
Aims

This paper describes the protocol for the first 2 phases of a knowledge translation and innovation project called AgeiNg in TechnologIcaLLy mEdiated Spaces (ANTILLES). Broadly, concepts of relational autonomy [57], relationship-centered care [58], apomediation theory (ie, the theory that peer supporters are pivotal in guiding individuals to relevant and credible health information) [59], and a positive psychosocial model of health and well-being in older adulthood [60] underpin this project. To help clarify initial causal assumptions, we depicted possible intervention pathways as a logic model (Figure 1). The model is based on a review by Allen et al [28] on LTC self-management support in online communities, which states that social ties formed in online communities can provide a basis for the performance of relevant self-management work and improve an individual's experience of living with an LTC.

The specific objectives are as follows:

1. Netnography component: explore the health and self-care topics that older people discuss in relation to LTC self-management and self-care in a publicly accessible online social media site and discussion forum.
2. Co-design component: identify and engage with stakeholders to define the needs and requirements for new ICT-based interventions to reduce social isolation and facilitate LTC self-management support for older adults living independently.

Figure 1. Theoretical model of pathways (logic model). LTC: long-term condition.



Methods

Study Design

We aim to use a two-phase approach, beginning with an in-depth qualitative netnographic study followed by a series of co-design workshops with health care consumers and service providers to synthesize design materials and propose novel ICT interventions.

Phase 1: Qualitative Netnographic Study

Data Collection

We will identify and analyze posts from online forums on a publicly accessible UK-based entertainment and lifestyle website and social network explicitly targeting older people. To identify the website, we searched Google using the advanced search function for online communities for older adults using combinations of keywords and Boolean operators, including "older*" OR "elder*" OR "senior*" OR "retiree*" AND "discussion*" OR "message board*" OR "forum*" OR "chat room*" AND "health." Websites were initially identified for inclusion in the study if (1) a stated objective of the website was to provide a platform for peer-to-peer communication among older adults or seniors or retirees about health-related topics, for example, through the hosting of chat rooms, email distribution lists, forums or message boards, and other interactive applications; (2) the website was in English and the materials posted by the users were publicly available and/or the users agreed that their information was nonconfidential and nonproprietary; and (3) the website was established (ie, operating for ≥3 months) and currently active (ie, forums are active and updated daily). The final host website and online community were selected according to several criteria of relevance, representativeness, heterogeneity, substance and critical mass of participants, activity and interactivity, data richness, and experiential features [42].

Textbox 1 provides a summary of the characteristics of the online discussion forum and the website's terms and conditions. Following earlier netnographic research [52], the name of the website was removed to protect the privacy of forum users. The website was chosen as the forum host as it is a popular website that presents posts and associated conversational threads publicly, thereby minimizing any ethical concerns related to *lurking* on online discussion forums. To locate relevant posts, we will access the online community forum and screen the *general health* discussion board for the 200 most recently active forum threads with posts including keywords generally related to older adults' self-care and self-management of LTCs in daily life. For the purpose of this study, we draw on the definition by

Grady and Gough [61] of *self-management* as "the day-to-day management of chronic conditions by individuals over the course of an illness"; *self-care* is defined as "tasks performed at home by healthy people to prevent illness, rather than merely managing existing illness." In addition, we will refer to the World Health Organization's (WHO) International Classification of Functioning, Disability, and Health framework and coding system to assist with the identification of posts related to discrete self-care or self-management tasks and environmental factors [62]. A record will be kept of the full URL for each thread that is downloaded so that it can be located again if it becomes necessary to refer back to the original webpage during data analysis or subsequent revisions before publication [25].

Textbox 1. Description of website and online discussion forum features.

Forum and website features

- The website hosts online forums on a range of topics, including education, travel, lifestyle (eg, gardening), health, finance, travel, and technology
- The website maintains an active presence on various social media platforms, including Facebook, Twitter, Instagram, and YouTube
- The forum is located within a UK-based entertainment and lifestyle website and social network for adults aged >50 years
- According to the forum's fact page, at the time of writing the manuscript (April 2020), the forum hosted 2051 topics with at least 22,201 posts
- Forums hosted on the website are publicly accessible for reading and posting via registration
- Forums support asynchronous discussion among users on conversational threads

User features

- Individuals using the discussion forum are known by a username only and the site does not enable users to contact each other privately
- Once users are registered with the site, they are solely responsible for all use and protection of the confidentiality of any user identification and password that they have selected or have been assigned for their access of the site
- User information is defined per the terms and conditions as "any information you provide to us or other users in relation to the service including the forums, blogs, advertising, selling, listing, buying or feedback processes, your postings on the message boards and any other content that you post on the Site"
- Users are solely responsible for their information; the website states that they act as a conduit only for web-based information, comments, advertising, distribution, and publication of users' information
- Any materials that users upload to the site will be considered nonconfidential and nonproprietary; the website has the right to use, copy, distribute, and disclose to third parties any such material for any purpose

Data Analysis

We will use Import.io, a data integration platform that enables automatic extraction of website contents, and download the messages into a Microsoft Excel workbook for storage and management. All textual and graphical materials will then be imported into the qualitative data analysis software package NVivo 12 (QSR International). In line with earlier qualitatively driven netnographic studies [56], we will analyze the data using a constructivist grounded theory approach [63] and elements of situational analysis [64], which extends the grounded theory to include different kinds of *maps* to explore differences and conceptual relationality. The analysis will move through 4 iterative stages: (1) open coding, (2) focused coding, (3) axial coding, and (4) theoretical coding. Extensive memo writing will accompany each step of the analysis. First, preliminary post-by-post and line-by-line open coding by 2 independent analysts across an initial subset of posts will generate a flexible coding framework, which will be iteratively revised as new codes are identified. This phase of the analysis will be concerned with inductively identifying, naming, categorizing, and describing phenomena, concepts, and properties of the data set. Focused coding will then be undertaken to synthesize and filter the preliminary codes or labels down into the most frequent and meaningful initial codes with regard to the research aims and questions. Then, we will conduct axial coding to develop a logical, coherent structure based on the identified codes and the relationships among codes (categories and properties). This process will result in the construction of a working, ordered, and semantic situational map [64]. Finally, we will undertake theoretical coding to refine and name core or superordinate categories, that is, higher-level categories subsuming within them the underlying characteristics of the phenomena of interest and the core concerns of the participants. Throughout this process, we will refer to analytical notes and memos containing reflections on emerging concepts and categories and undertake a constant comparison between focused coding. In our presentation of the results, quotations will be reproduced verbatim, retaining original spelling and grammatical errors, emoticons or emoji, and formatting. We will replace usernames with unique alphanumeric identifiers (eg, the third participant in the second thread of forum 1 will be identified as F1-T2-P03) and apply these to all associated data, including analytic memos, images, and other saved files. NVivo will be used to conduct digital open and focused coding. We will combine this approach with manual methods (eg, note taking, sticky notes, large format display boards) to facilitate a constructivist approach to generate the grounded theory [65]. Mindful of the privacy of forum users, we will not seek respondent validation of the study findings. The anonymous nature of online forum profiles may make it difficult to obtain complete and accurate sociodemographic information about forum users. Although it is possible to derive some personal information (eg, age, gender, marital status) from the posts, this information is not guaranteed to be accurate.

Rigor

We will employ an observational approach to netnography, comparable with qualitative studies of naturalistic interactions in online discussion forums [40]. A *passive* researcher role was deemed most appropriate for the exploratory phase of the research because of its emphasis on exploring the aspects of generating an understanding of online cultures, knowledge exchange, peer interaction, and learning to inform knowledge translation and co-design of digital solutions. Nonparticipatory (passive) netnographic approaches have been criticized because of concerns regarding privacy and the lack of opportunity for researchers to conduct their research in ways that directly contribute value to online communities [66,67]. To overcome this limitation, we will record our personal reactions as reflexive field notes while continuing to gain familiarity with the language and practices of the online forum, seeking further stakeholder input in the next phase of the study to clarify understandings or meaning and to contextualize the research findings to the areas of application. Subsequent co-design workshops with stakeholders will provide further context grounded in the diverse experiences and perceptions of current and potential users of online health communities.

We will refer to the Consolidated Criteria for Reporting Qualitative Studies checklist [68] to guide the documentation and reporting of our findings in consideration of credibility, dependability, and transferability. We will demonstrate credibility and dependability by collecting data over a period of 4 to 6 months and by detailing our research processes through an audit trail of methodological and interpretative decisions at each stage of the analysis. We will enhance transferability by describing in detail the original context of the research (ie, documenting characteristics of the website) and providing a detailed account of the processes and nature of the data collected.

Phase 2: Co-Design Workshops

Following the netnographic study, we will engage with stakeholders in a series of co-design workshops to (1) discuss the findings of the netnography and deepen our understanding of the perspectives of older people, carers, and service providers toward opportunities and limitations of participating in online social networks for LTC self-management support and (2) define the needs and requirements for new ICT interventions to address social isolation and support LTC self-management. We will use an iterative co-design approach [69,70] employing aspects of experience-based co-design (EBCD) [71] and drawing on techniques applied successfully in previous health technology co-design [72,73]. This approach generally involves stakeholders (eg, staff, patients, and family carers) reflecting on their experiences of using a service or product to collaboratively identify priorities for improvement and to suggest modifications. Co-design workshops are increasingly used in participatory design to help developers and stakeholders share perspectives, and such approaches have been used widely in health service redesign initiatives [69,70]. Co-design principles have been applied in technology-oriented research to ensure that technologies and the services in which they are embedded evolve together, grounded in the needs and experiences of consumers who are engaged in the design process [74]. The ability to incorporate user narratives through stories and the use of specific scenarios can provide a focus for communicating design concepts and how they might be used [75,76].

Sample and Procedure

We will conduct 3 co-design workshops with stakeholders, including health and social care providers, carers, and older adults independently living (aged ≥65 years) with lived experience of managing an LTC (assessed using a demographic survey). We anticipate that approximately 8 to 10 people will attend each workshop (number of attendees, N=15-30). In addition to these end-user and user community representatives, we identified the following stakeholders for inclusion in our wider design deliberations: (1) project team members, university staff investigators in the research project; (2) external stakeholders, academic clinicians supporting the research; and (3) solution domain experts, independent university staff and technical staff with experience in using or developing ICTs for older adults. Workshop participants will be recruited through the research team's established network of academic clinicians and a formal process facilitated by a consumer organization working with older South Australians. Participants will be representative of a range of health conditions, sociodemographic characteristics, and experiential, gender, and ethnic diversity. All workshop participants will have some (direct and indirect) experience of using or assisting someone to use ICTs for health-related purposes. We will only include stakeholders who are able to provide informed written consent and communicate sufficiently well in English, as we cannot guarantee the presence of an interpreter during the workshops. The workshops will be facilitated through a South Australian research and product development center co-located with Flinders University that specializes in involving users in co-design and innovation initiatives that respond to global population aging. Remote videoconferencing will be made available in the event of continued COVID-19 disruptions [77].

The aim of the first 2 workshops, conducted with consumers and service providers separately, is to identify goals, define problems, and determine the assumptions to be tested in relation to the following 4 broad questions:

1. What is lacking in the current digital services for older people with LTCs living in the community who experience social isolation?
2. What do we want the solutions to ideally achieve?
3. How can we imagine the solutions failing?
4. Who will be involved in using the solutions?

These questions to be addressed were informed by previous community-based participatory research, including co-design workshops [69]. In the third joint workshop, representatives from both groups will be brought together to discuss solutions and prioritize functions and content. At the beginning of workshops 1 and 2, we will give a short presentation to give background information about the research. We will then screen a brief *trigger film* to each group, derived from our earlier qualitative research [78], to stimulate discussion and support the identification of improvements grounded in authentic consumer experiences. Although conventional EBCD specifies

that films can be created with service users and providers at the sites of delivery, our use of the trigger film enables a more efficient process and may also be less threatening to health care providers than appearing to critique existing services [71,79]. Then, drawing on the future workshop approach in participatory design [72], in the initial ideation workshop, participants will discuss existing technologies and services and propose their own imagined solutions, considering features of the existing services that could be adapted, expanded, or repurposed. In the following session, these ideas will be presented in the initial prototypes for critique and collective refinement (Table 1). To help older people engage more authentically and democratically in the co-design process, we will employ visual aids (eg, flow diagrams, card prompts) and various facilitated interactive tasks to help focus attention and facilitate discussion on specific aspects of the design [73,80,81].

Table 1. A summary of the co-design workshop procedure and materials.

Characteristics	Workshops 1 and 2	Workshop 3
Sample and procedure	• Older adults and carers only participate in initial ideation workshop (workshop 1) to discuss materials and propose solutions • Service providers only participate in initial ideation workshop (workshop 2) to discuss materials and propose solutions	• Joint workshop bringing representatives from both groups together to discuss synthesized materials and critique prototypes
Materials	• *Trigger film* is screened at the beginning of each workshop to stimulate discussion grounded in authentic consumer experiences, followed by persona • Persona to be used to provide a shared focus for identifying solutions	• Discussion of scenarios derived from synthesis of outputs from workshops 1 and 2 • Critique and refinement of specific intervention suggestions
Outcomes	• Clarification of goals, problem definition, and assumptions to test • Identification of priorities to be discussed in subsequent sessions • Generation of scenarios describing prototype interventions	• Refinement of initial ideas captured in scenario materials into specific solutions • Summary of key issues arising from each workshop in joint display

A secondary aim of this component of the study is to explore whether the design materials presented and developed in the workshops could be utilized to provide a synthesis of key research findings. We will develop a *persona*, intended to be an archetypal narrative description of potential users of a product or service, that will be used to reflect the key characteristics or experiences that need to be taken into consideration when proposing improvements to the current services [82]. To help generate a persona that adequately synthesizes existing research into carers' and older adults' perspectives, we draw on the findings from phase 1 of the study and systematic reviews of community-dwelling older adults' care and support needs [1,14,83]. We will also refer to guidance on developing vignettes or *composite narratives* (ie, an overarching narrative reflective of core aspects of diverse patient experiences) [84] to explore complex public health issues in qualitative research [85]. In line with the prototyping approach used in future workshop methodology, we will then use suggestions raised in the initial workshop to generate *scenarios* [86] describing potential interventions in practice. As scenarios involve action-based narratives, they are more suited than personas for encouraging consideration of the acceptability and feasibility of the proposed solutions and their implementation in the local context [71]. Before workshop 3, the suggestions from workshops 1 and 2 will be synthesized into prototype interventions. By the end of the third workshop, the initial ideas captured in the scenario materials will be refined into specific solutions.

Data Analysis

We will obtain consent from all workshop participants to be audiorecorded for research purposes. These recordings will be professionally transcribed and analyzed inductively and thematically using a constant comparative method [87]. Using this approach, transcripts and reflective field notes taken during and immediately after the workshops will be first broken down into concepts and then grouped into categories to summarize key issues arising from each workshop. The authors will review field notes and share their impressions after each workshop so that emerging issues can be discussed and explored in subsequent sessions. Data will then be combined, integrated, and presented visually in a joint display [88] to provide a summary of emerging themes for older adults, carers, and service providers. The results of the netnography will also be presented in an information visualization (eg, an infographic) to help communicate the research findings to diverse audiences.

Quality Validation

Owing to the exploratory nature of this research and its focus on emergent co-creation through multistakeholder engagement, we did not prespecify any specific interventions or outcome measures. Although such prespecification is a quality feature in conventional study protocols, it could be considered inappropriate and potentially counterproductive in co-design research [89,90]. This is because, by definition, the specific intervention and its application in the local context are yet to be determined. To ensure credibility and relevance, we plan to codetermine the nature and delivery of the intervention and how its outcomes are measured with stakeholders while concurrently

developing research capacity in community partners, establishing program governance, building trust, and working through potential disagreements. In co-design and implementation research, these processes are considered to be mutually reinforcing [89]. Finally, we acknowledge that compromises may have to be made to the proposed methodology to preserve relationships and partnership synergy and to improve impact.

Ethical Considerations

Ethical approval was obtained from the Flinders University Social and Behavioral Research Ethics Committee (project number 8559). In phase 1, as the identities of users are unknown (people posting on the website are known only by their username), we were unable to obtain informed consent from individual users to participate in the research. Consistent with contemporary guidelines and ethical codes of conduct for conducting web-based studies [91,92], the first author approached the website via email and obtained permission in October 2019 from the website to use their data, including any text (discussion forum posts and replies) and accompanying visuals for the project period. To enhance transparency, we will advertise and explain the research on the website, Facebook page, and Twitter feed of the website before commencing the study. To further protect the privacy of website users, we will remove terms, images (if attached in forum posts), and phrases that could identify users, their health care providers, and/or carers.

Results

Data collection for the first phase of the study began in April 2020, approximately 100 days after the WHO was notified of the first cases of COVID-19 in China's Hubei province [93]. We plan to collect data (ie, forum posts and responses in relevant discussion threads) continuously until October 2020 using observational netnography techniques. The second phase of the study will commence in late 2020 and will be completed by the end of 2021.

Discussion

Understanding the content and functioning of peer-to-peer interaction in online health communities is critical to the development of ICT-based interventions that are credible, relevant, and meaningful to community-dwelling older people and their supporters. To our knowledge, this study is the first to apply qualitative netnographic and co-design methods to address LTC self-management support for older adults. This study has several outcomes and implications. First, as one of the few studies of older adults' peer-to-peer health communication in online communities [11,23,48,56], this study will generate practical and potentially transferrable knowledge about the types of health and self-care support that older adults seek and receive from peers on the web and how other users respond to such queries. These insights could be used in future research to inform the design of peer-based web-based interventions and health communication campaigns involving strategic and targeted messaging [94,95].

Second, this study will offer additional learning about how the aspects of EBCD can be integrated with other techniques successfully applied in health technology co-design. One example in this study is the future workshop method, which provides an *early-stage option* [71] for initial idea generation, critique, and refinement, preceding and informing technology coproduction. The use of design materials (ie, persona and scenarios) provides a vehicle for translating research knowledge into reusable and accessible consumer experience resources [84]. Although the selective adoption of multiple co-design approaches and techniques originating from different fields of research can pose a challenge to fidelity, we have attempted to delineate and justify the chosen elements from each. In addition, we acknowledge that the proposed workshops are not a substitute for the need for continued engagement with health care consumers, service providers, and technology industry representatives to fully develop and formally evaluate the intervention.

Third, the study will provide insights into the potential of ICT-based interventions involving open and autonomous online communities (ie, communities created and used mostly by members of the public), which has been identified as "an area in need of and ripe for future study" [15]. For example, social media–based interventions, including forum moderation aimed at stimulating discussion, correcting misinformation as needed, and protecting user safety, might influence the trajectory and quality of web-based peer interaction and enhance users' self-care confidence and capabilities. Clinical applications could include health professionals' vetting of and referral to online social media–based peer health groups among their older patients and their carers as a supplementary source of support and/or for patient outreach and extended care [15,23]. Such an approach could extend the benefits of online community participation to the broader population of community-dwelling older adults, while mitigating misgivings about safety and misinformation. This is particularly relevant given the finding that users of online health communities frequently receive support from peers in relation to their unmet needs that they are unable to obtain through their interactions with health care providers and/or their informal carers [15]. Finally, the findings from this study could inform the development of more purposeful design interfaces and educational strategies to address older people's social isolation and support LTC self-management and self-care in the contexts of limited formal and informal (in-person) care support, during and after the COVID-19 pandemic.

Conclusions

As countries worldwide grapple with the unparalleled challenges caused by the COVID-19 pandemic, social isolation among community-dwelling older people and the impact of interrupted care and support on LTC management are being recognized as pressing public health concerns [8]. The proposed study addresses this issue by exploring online communities as a medium of peer-to-peer health communication and by engaging with stakeholders to collaboratively develop a novel ICT-based intervention to provide informational and social support networks. The findings from this study will inform the next coproduction and evaluation phase of the ANTILLES project

and will have implications for digital health promotion related to social support, LTC self-management and self-care, and peer education and support strategies.

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Authors' Contributions

ML, the principal investigator, conceptualized the study, designed the protocol, and drafted the manuscript. MA, MP, PD, and AK provided intellectual background with regard to the aims, underpinnings, and study design and contributed to the writing and editing of the manuscript. All authors approved the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ANTILLES: AgiNg in TechnologIcaLLy mEdiated Spaces
EBCD: experience-based co-design
ICT: information and communication technology
LTC: long-term condition
WHO: World Health Organization

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Protocol

The Impact of Dietary Protein in Complementary Foods on Infant Growth and Body Composition in a Population Facing the Double Burden of Malnutrition: Protocol for a Multicenter, Prospective Cohort Study

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Abstract

Background: Protein is an essential macronutrient with an important role during complementary feeding. Low protein intake contributes to undernutrition while high intake, especially from animal sources, may increase obesity risk. However, the influences of different protein sources (dairy, meat, and plants) on growth, and underlying mechanisms for these effects, are poorly understood. Animal-sourced foods provide both high-quality protein and iron and are recommended to improve iron status. However, it is unclear whether current dietary recommendations are adequate to support healthy growth and optimize iron status. These issues are of particular concern in countries facing the double burden of malnutrition, the coexistence of all forms of malnutrition. More evidence is needed to develop appropriate recommendations for these countries.

Objective: This study will investigate associations between protein intake during complementary feeding and growth, body composition, and iron status of infants in Thailand, a country facing the double burden of malnutrition. The study will also explore how different protein sources influence growth via the growth hormone—insulin-like growth factor I (IGF-1) axis and plasma amino acids.

Methods: A multicenter cohort study will be conducted in Chiang Mai, Thailand, in 150 healthy term infants aged 4-6 months with birth weight ≥2500 g. Demographic data, dietary intake, and anthropometry will be collected at 6, 9, and 12 months. Dietary intake will be assessed using 24-hour dietary recalls, 3-day food records, and food frequency questionnaires. Blood samples for iron status, growth hormone, IGF-1, insulin-like growth factor-binding protein III (IGFBP-3), and plasma amino acids and urine samples for body composition analysis using stable isotope dilution will be obtained at 12 months.

Results: The recruitment of study participants and data collection was undertaken from June 2018 to May 2019. Data and laboratory analyses are ongoing and are expected to be completed by December 2020. A total of 150 participants were enrolled, and 146 completed the study. We hypothesized that protein intake from animal-sourced foods in recommended quantities could support normal weight and length gain and lower the risk of undernutrition associated with similar amounts of plant-based protein. However, higher protein intake, especially from milk protein, may be linked to increased body fat via plasma amino acids and the growth hormone-IGF axis.

Conclusions: The results of this study will provide data on current complementary feeding practices, focusing on protein and iron intake in Thai infants. This information, combined with data on associations with infant growth and iron status, will help inform complementary feeding recommendations for this population and may be found relevant to other settings experiencing the double burden of malnutrition.

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KEYWORDS

complementary feeding; protein intake; double burden of malnutrition; infant growth; body composition

Introduction

In 2016, while 52 and 155 million children around the globe were suffering from wasting and stunting, 41 million children under the age of 5 years were overweight or obese [1]. Therefore, the United Nations General Assembly launched a new policy, the United Nations Decade of Action on Nutrition from 2016 to 2025. The policy aims to end hunger and eradicate all forms of malnutrition worldwide [1]. In this proclamation, the double burden of malnutrition, the coexistence of undernutrition, overweight, obesity, and diet-related noncommunicable diseases are highlighted as an emerging public health problem in many countries experiencing socioeconomic transition. In order to achieve the goals of the proclamation, early life nutrition, especially during the first 1000 days of life, has been identified as one of the primary targets of intervention [2].

Along with optimal maternal nutrition and exclusive breastfeeding until 6 months of age, complementary feeding plays a pivotal role in early life nutrition from the age of 6 to 24 months. This period is also the most challenging, as a systematic review indicated that no single intervention can optimize growth outcomes for infants living in different circumstances with variations in the availability of micronutrient-rich foods, degree of household food insecurity, and traditional complementary feeding practices [3]. Among various topics related to complementary feeding, dietary protein is interesting as it is linked to all forms of malnutrition.

Protein is an essential macronutrient needed to build organ systems and body structures and mediates many physiological functions throughout life. For infants and young children, protein requirements per kg body weight are higher than any other age groups due to their rapid growth [4]. In addition, the proportion of energy from protein abruptly changes from 5% to around 15% of total energy intake when breastfed infants are introduced to complementary foods [5]. According to current evidence, insufficient protein intake during complementary feeding can contribute to undernutrition [6-8], whereas too much may increase the risk of overweight and obesity in later life [9-13].

Nevertheless, it is not only the amount of dietary protein that matters but also the source. Dietary protein comes from either animals or plants. Some studies have shown a link between protein sources and growth via plasma amino acids and the growth hormone—insulin-like growth factor I (IGF-1) axis. Semba et al demonstrated that stunted children had lower levels of plasma essential amino acids [14]. In contrast, a multicenter randomized controlled trial in 5 European countries showed that plasma Leucine and IGF-1 were positively associated with body mass index z-score (BMIZ) in infants who received high protein intake from infant formula [15]. These findings have two important implications. First, protein from animal-sourced foods such as milk, meat, and eggs provides all essential amino acids, while plant-based proteins (cereals, legumes, vegetables) usually lack one or two essential amino acids. Thus, it can be assumed that the effect of dietary protein on growth is more closely related to protein source than quantity. Second, as the proportion of leucine in the amino acid content of whey is higher in milk than that in meat (14% vs 8%, respectively) [16], protein intake from nondairy animal-sourced foods may not have the same influence on BMIZ as similar intake from milk. However, few studies have measured body composition as it relates to the intake of different protein sources.

Most evidence comes from two separate paradigms. The first has focused on lower- and middle-income countries where the researchers try to encourage higher protein intake in terms of both quantity and quality to overcome undernutrition, while the second paradigm is emerging in higher-income settings where researchers are aiming to prevent obesity by reducing the protein intake of infants and young children. As a result of these separate approaches, it is difficult to define guidelines for countries that are now facing the double burden of malnutrition, the majority of which are low- to middle-income countries.

Thailand is a country facing the double burden of malnutrition. The latest national and international surveys demonstrate a slowly declining percentage of childhood stunting, a high prevalence of iron deficiency, and rapidly increasing proportions of overweight, obesity, and diet-related noncommunicable diseases at a population level [17-19]. However, there have been no recent studies on protein intake among Thai infants. Although the latest Thai dietary reference intakes recommend a protein intake of 1.56 g/kg/day for Thai infants aged 6-11 months [20], there have been no clinical studies to support the adequacy of this recommendation in Thai infants as the recommendation is adapted from international guidelines [4].

Aims and Hypotheses

We aim to understand the impact of dietary protein in early life using a holistic approach. This study will fill some of the knowledge gaps related to underlying mechanisms through the following objectives and hypotheses:

1. We will investigate the associations between the amounts and sources of dietary protein typically provided to Thai infants aged 6 to 12 months and changes in growth, including weight-for-age z-score (WAZ), weight-for-length z-score (WLZ), length-for-age z-score (LAZ), and BMIZ over 6-12 months. We will test the hypothesis that protein intake from animal-sourced foods in recommended quantities can support normal weight and length gain and reduce the risk of undernutrition associated with similar amounts of plant-based protein.

2. We will investigate the associations between the amounts and sources of dietary protein typically provided to Thai infants aged 6 to 12 months and body composition at 12 months of age. We will test the hypothesis that a higher intake of protein from animal-sourced foods, especially dairy protein, is associated with an increased proportion of body fat during infancy.
3. We will investigate the associations between complementary foods that provide different amounts of protein from animal-sourced foods and plant-based diets typically provided to Thai infants aged 6 to 12 months with iron status at 12 months of age. We will test the hypothesis that the timely introduction of protein from animal-sourced foods, especially red meat in the recommended amount, is associated with improved iron status and lower risk of iron deficiency anemia, without increasing the risk of overweight/obesity.
4. We will investigate the possible mechanisms linking dietary protein and growth in early life through metabolomic processes. We will test the hypothesis that high protein intake from animal-sourced foods is associated with increased plasma essential amino acids, which may be correlated with concentrations of growth hormone, IGF-1, and IGFBP-3.

Methods

Study Design and Approval

Study Design

This protocol is for a multicenter, prospective cohort study.

Study Setting

This cohort study will be performed in three well-baby clinics in Chiang Mai, Thailand. We selected these well-baby clinics based on their locations and opening times that did not overlap, allowing the single investigator to attend all clinic sessions. Two study sites are in urban areas, and another is in a suburban area. One clinic in the urban area is in a maternal and child-friendly hospital where infant formula is prohibited, and the breastfeeding rate is higher than the average for other Thai hospitals.

Ethics Approval

The study will be conducted in accordance with the Declaration of Helsinki. Participation is voluntary, and subjects can withdraw from the study at any stage. The study enrolment is completed when written informed consent is obtained from the legal guardian. Identifiable data of participants and their families will be kept in a secure location, only accessible to the researchers. Ethics approvals have been obtained from the University College London Ethics committee, United Kingdom (Approval ID: 12551/001), and the Ethics Committee of the Faculty of Medicine, Chiang Mai University, Thailand (Approval ID: PED-2561-05287).

Definitions

Key terms are defined in Textbox 1.

Textbox 1. Definitions.

Complementary feeding is all solid and liquid foods other than breast milk or infant and follow-on formula, as suggested by the European Food Safety Authority (EFSA) [21] and the position papers from the European Society for Pediatric Gastroenterology Hepatology and Nutrition [22].

Stunting is defined as LAZ <2 SD below the median of the WHO growth standards for children aged under 5 years [23].

Wasting is defined as WLZ <2 SD below the median of the WHO child growth standards for children aged under 5 years [23].

Underweight is defined as WAZ is <2 SD below the median of the WHO child growth standards for children aged under 5 years [23].

Overweight is defined as WLZ >2 SD above the median of the WHO child growth standards for children aged under 5 years [24].

Obesity is defined as WLZ >3 SD above the median of the WHO child growth standards for children aged under 5 years [24].

Iron deficiency is defined by at least one of the following serum ferritin less than 12 µg/L (if erythrocyte sedimentation rate, ESR ≤10 mm/h) or serum ferritin less than 30 µg/L (if ESR >10 mm/h) or serum transferrin saturation less than 16% [25].

Iron deficiency anemia is defined as iron deficiency plus hemoglobin <11.0 g/dL [25].

Exclusive breastfeeding means the infant receives only breast milk without anything else except for water and necessary medication.

Predominant breastfeeding means that breast milk is more than 50% of daily milk intake after 6 months of age.

Predominant formula feeding means that infant or follow-on formula provides more than 50% of daily milk intake and for a longer period than breastfeeding.

Animal-sourced food is defined as any food that is edible and originates from animals such as milk, dairy products, meat (ie, beef, pork, poultry), processed meats, fishes, insects, and eggs.

Plant-based protein is defined as dietary proteins that are edible and originate from plants such as cereals, lentils, legumes, nuts, and vegetables.

The *primary caregiver* is defined as the person who spends the most time looking after the infant on a daily basis.

Study Population

Inclusion Criteria

Eligible infants are full-term (gestational age ≥37 weeks), healthy, singleton infants aged 4-6 months whose birth weight was ≥2500 g.

Exclusion Criteria

Infants with any underlying or chronic diseases, those with a known case of, or recovery from, protein-energy malnutrition, and infants regularly receiving medication except mineral and vitamin supplementation will be excluded.

Participant Selection and Recruitment

Parents or caregivers of infants aged 4-6 months who are eligible for the study will be approached by a researcher when they routinely visit the well-baby clinic and asked if they are interested in taking part in the study. The researcher will give the parent an information sheet and answer all queries on a case by case basis. If they consider participating, contact details will be obtained. After 48 hours, the researcher will call the parents to ask if they wish to take part and, if they agree, the first appointment will be scheduled. At the first visit, informed consent will be signed by the parent or legal guardian who is the primary caregiver of the participant.

Data Collection

There are 3 visits at the well-baby clinic for each participant when they are 6, 9, and 12 months of age (Table 1).

Table 1. Data and collection of biological samples.

Data collection	First visit, age 6 months	Second visit, age 9 months	Third visit, age 12 months
Demographic data	• Family type, family income (monthly), primary caregiver • Parental education and occupation • Parental body weight and height • Prenatal screening and problems • Mode of delivery, gestational age at birth, birth weight, length, and head circumference • Postnatal problems (eg, neonatal jaundice)	• N/A[a]	• N/A
Milk feeding	• Type of milk feeding, duration of exclusive breastfeeding	• Type of milk feeding, duration of breastfeeding/using breast milk	• Type of milk feeding, duration of breastfeeding/using breast milk
Dietary intake	• Age of first introduction of complementary feeding, type of first complementary feeding, age of introducing each type of diet (cereal, meat, egg, milk) • 24-hour dietary recall • Food Frequency and Baby Eating Behavior Questionnaire	• Age of introducing each type of diet • 24-hour dietary recall • 3-day food record • Food Frequency and Baby Eating Behavior Questionnaire	• Age of introducing each type of diet • 24-hour dietary recall • 3-day food record • Food Frequency and Baby Eating Behavior Questionnaire
Anthropometric measurements	• Bodyweight, length, head circumference, mid-upper arm circumference	• Bodyweight, length, head circumference, mid-upper arm circumference	• Bodyweight, length, head circumference, mid-upper arm circumference
Biological sample collection	• N/A	• N/A	• Blood sample: 5 ml venous blood • Body composition: 1.5 mL urine × 3 samples, before and after dosing with Deuterium oxide
Other information	• Feeding problems, acute illness	• Feeding problems, acute illness	• Feeding problems, acute illness

[a]N/A: not applicable.

Biological Sample Collection, Preparation, and Storage

Blood Samples

At 12 months of age, a venous blood sample will be obtained by experienced nurses or health professionals. Five milliliters of venous blood will be separated into 4 collecting tubes; 1 EDTA tube for ESR and plasma amino acids, 1 EDTA microtainer for complete blood count (CBC), 1 clotted blood tube for growth hormone, IGF-1, IGFBP-3, and 1 heparinized microtainer for serum ferritin, serum iron, and serum total iron-binding capacity. The blood samples for CBC, ESR, serum ferritin, serum iron, and total iron-binding capacity will be analyzed on the day of blood collection. The rest of the blood samples for growth hormone, IGF-1, IGF-binding protein 3 (IGFBP-3), and plasma amino acid analysis will be centrifuged

and aliquoted into cryovials within the same day and stored at –80°C until analysis.

Urine Samples

Infant body composition will be measured by the isotope dilution technique using deuterium oxide (^2H_2O). At 12 months of age, the dose of deuterium oxide calculated according to infant body weight (0.1 g per kg ^2H_2O body weight) will be prepared as a solution (in water, juice, or milk) and orally administered to infants during their final visit. Urine samples will be obtained before dosing and after dosing at 6 and 24 hours. Urine samples will be stored at –80°C until analysis.

Study Outcomes

Primary Outcome

The primary outcome measure will be the conditional change of growth parameters (WAZ, WLZ, LAZ) from 6-12 months of age.

Secondary Outcomes

Secondary outcome measures will be (1) the conditional change of BMIZ from 6-12 months of age, (2) anthropometric measurements at 12 months of age, (3) infant body composition at 12 months of age, (4) iron status including CBC, serum ferritin, SI and total iron-binding capacity at 12 months of age, (5) growth-related hormones (growth hormone, IGF-1, IGFBP-3) at 12 months of age, and (6) plasma amino acids at 12 months of age.

Outcome Measures

Energy and Nutrient Intake

Dietary data will be collected using 24-hour dietary recalls and the Food Frequency Questionnaire at 6, 9, and 12 months and 3-day food records at 9 and 12 months. All dietary data will be converted to energy and nutrient intake (ie, carbohydrate, fat, protein, calcium, phosphorus, iron, zinc, vitamin B1, vitamin B2, vitamin C, and vitamin A) by using the Institute of Nutrition Mahidol University Calculation program version 4.0 developed by the Institute of Nutrition, Mahidol University, Bangkok, Thailand [26]. This program reports total protein and iron intake from both animal and plant sources. Breastfeeding will be recorded as frequency and duration (minutes per meal) each day, then the volume of breast milk will be estimated using the average amount from two algorithms [27,28].

Anthropometric Assessment

Bodyweight will be measured using calibrated electronic scales accurate to 0.01 kg and recumbent length using a standard wood board accurate to 0.1 cm. The SD z-scores for weight-for-age, length-for-age, weight-for-length, and BMI will be calculated using WHO software (WHO Anthro version 3.2.2) based on the 2007 WHO Growth Standard [29]. Although the WHO recommends weight-for-length to be used to determine wasting and overweight for children aged <2 years, a recent study showed that infant BMI had a higher positive predictive value than weight-for-length for childhood obesity [30].Therefore, the present study will measure both indices.

Dietary Data Collection Tools

The format of the 24-hour dietary recalls and 3-day food records have been adapted from Lanigan et al [27] and translated into the Thai language by the researcher who is a Thai native speaker. The semi-quantitative Food Frequency Questionnaire was developed with information on food items consumed by Thai infants and toddlers aged 0-3 years relating to the food consumption data of Thailand 2016 [31]. The Food Frequency Questionnaire contains 130 food items. Appetite traits will be evaluated by the Baby Eating Behavior Questionnaire, which was developed by Llewellyn et al from the Gemini birth cohort [32].

Laboratory Analyses

Infant Body Composition

Urine samples will be measured by isotope-ratio mass spectrometry (Gasbench-Delta XP system, Thermo Fisher Scientific, Bremen).

Iron Status

CBC will be analyzed by using an automated hematological analyzer (Sysmex XN 9103, Sysmex UK). An automated system will be used for the direct determination of ESR (VES-MATIC cube 30, DIESSE Diagnostica Senese). Serum ferritin, serum iron, and total iron-binding capacity will be analyzed by using a chemiluminescent method (Cobas modular analyzer, Roche Diagnostics, F Hoffmann-La Roche, Germany).

Growth-Related Hormones

Growth hormone, IGF-1, and IGFBP-3 will be analyzed by enzyme-linked immunosorbent assay (IMMULITE 2000, Siemens Healthcare Diagnostics Products).

Plasma Amino Acids

Twenty plasma amino acids will be analyzed by using the high-performance liquid chromatography (Biochrom30 amino acid analyzer, Biochrom).

Statistical Analysis

There are two main parts of the statistical analysis. First, we will summarize the population characteristics of milk feeding, complementary feeding, and prevalence of undernutrition, overweight/obesity, and iron deficiency. Second, we will examine the associations between protein intake and source during complementary feeding and the outcomes specified in the objectives and hypotheses. All statistical tests will be considered significant when the *P* value is <.05 or 95% CIs of odds ratios do not include 1.

Descriptive data will be presented as mean (SD), median with interquartile range, or percentages depending on data type and distribution. These data will include demographic characteristics of infants and families, breastfeeding rate, age of the first introduction of complementary feeding, details of complementary feeding and energy/nutrient intake at each time point, average growth parameters at each time point, growth trajectory, and the prevalence of malnutrition (including wasting, stunting, overweight/ obesity, iron deficiency, iron deficiency anemia).

Protein intake at each time point, both total and separated by dietary source (ie, dairy protein, nondiary animal-based protein, and plant-based protein), will be considered as primary predictors to examine associations between protein intake and outcomes. To investigate associations between those predictors and continuous outcomes such as growth z-scores, percentage of body fat/fat-free mass, and blood parameters, we will use linear regression and correlation models (Pearson or Spearman correlation) for either univariate or multivariate analysis. For multivariate analysis, covariates will be selected for each of the dependent outcomes from previous research publications and our univariate analyses. Additionally, we intend to apply the directed acyclic graphs identifying covariates to reduce confounders [33]. If the dependent outcomes are categorical data such as nutritional status or iron status, binary or logistic regression analysis will be used as the main models.

The study aims to reduce the bias of baseline body size of individual infants on growth outcomes by using conditional growth. This method captures how an individual child deviates from the average growth trajectory in the population, taking into account overall regression to the mean, and expresses growth acceleration or deceleration in an individual relative to this population growth pattern. For example, if the conditional weight z-score is positive, we can interpret that the infant has shown more rapid weight gain than others in the population who had the same baseline size [34]. Therefore, the conditional change in growth parameters from 6 to 12 months will be calculated using linear regression of weight/length z-scores at 12 months on baseline values at 6 months. Residuals from the model represent the difference between observed and predicted growth over this period.

We will use data from the standard recommendations, previous research, and our own data to determine the most appropriate cut-offs for low or high protein intake. We will then compare the outcomes between these groups.

Sample Size Calculation

We used the two-different means formulae [35] to calculate the sample size required to detect a 0.5 SD difference in growth parameters (WAZ, WLZ, and LAZ) between infants who receive red meat frequently and less frequently from 6-12 months of age (Textbox 2).

Textbox 2. Sample size calculation.

- Mean difference 0.5 SD
- SD 1.0 (adopted from Olaya G et al [36])
- Power 80%, significance level .05
- Sample size: 126 participants
- With surplus 15% drop out rate, the final number is 148 participants

Results

Recruitment commenced in June 2018 and was completed in October 2018. Data collection was completed in May 2019. Laboratory analyses are ongoing and are expected to be complete by December 2020. Initially, 150 infants were enrolled, and only 4 (3%) had dropped out at the end of the data collection period. The results of this study will be presented and disseminated through peer-reviewed journals and academic conferences.

Discussion

Thailand has highlighted early life nutrition as a window of opportunity to overcome the double burden of malnutrition [37]. Several campaigns from the Thai government have been launched to improve maternal and infant nutrition. Examples include a program that encouraged supplementation of Triferdine, which consists of iron, iodine, and folic to women of child-bearing age, promotion of exclusive breastfeeding until 6 months of age as well as iron supplementation of infants and young children aged 6 months to 2 years [38]. However, there is no specific campaign related to complementary feeding and, to the best of our knowledge, no recent studies in this field.

Although recommendations should ideally be based on experimental data, the lack of recent data on dietary protein intake and growth outcomes in Thai infants precluded the development of a practical intervention that could be tested in a randomized controlled trial in this population. To address this issue, we decided to adopt a sequential approach in 3 consecutive studies, beginning with a descriptive study to gather information on the attitudes, knowledge, and practices related to complementary feeding in Thai families. This study provided a clearer picture of complementary feeding among Thai parents and highlighted interesting findings that were used in the design of the current prospective cohort study [39]. For example, rice porridge and mashed banana were the most common first foods for Thai infants with or without a small amount of egg yolk. Some Thai parents delayed providing animal-sourced foods to their children and had concerns that such foods were difficult to digest and had high allergenicity compared with plant-based proteins.

The second phase of our research consists of the observational study described here, incorporating the findings of our previous study. The aim is to investigate the intake of different protein sources during complementary feeding and associations between protein intake and growth outcomes, body composition and iron status in the same population, as well as to investigate possible mechanisms related to those associations. The results of this study may be used to plan the third phase of our research, testing an intervention to improve growth and iron status in this infant population.

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Authors' Contributions

KK, MF, and JL were responsible for identifying the research questions, forming the hypotheses, and planning the study protocol. JW provided advice on technique and sample preparation for body composition analysis. KK wrote the manuscript with input from all coauthors. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

BMIZ: body mass index z-score
CBC: complete blood count
DBM: double burden of malnutrition
ESR: erythrocyte sediment rate
IGF-1: insulin-like growth factor I
IGFBP-3: insulin-like growth factor-binding protein III
LAZ: length-for-age z-score
WAZ: weight-for-age z-score
WLZ: weight-for-length z-score

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Protocol

Impacts of Motion-Based Technology on Balance, Movement Confidence, and Cognitive Function Among People With Dementia or Mild Cognitive Impairment: Protocol for a Quasi-Experimental Pre- and Posttest Study

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Abstract

Background: While exercise can benefit the health and well-being of people with dementia or mild cognitive impairment, many exercise programs offered to this population are passive, unengaging, and inaccessible, resulting in poor adherence. Motion-based technologies are increasingly being explored to encourage exercise participation among people with dementia or mild cognitive impairment. However, the impacts of using motion-based technologies with people with dementia or mild cognitive impairment on variables including balance, movement confidence, and cognitive function have yet to be determined.

Objective: The purpose of this study is to examine the impacts of a group motion-based technology intervention on balance, movement confidence, and cognitive function among people with dementia or mild cognitive impairment.

Methods: In this quasi-experimental pre- and posttest design, we will recruit 24 people with dementia or mild cognitive impairment from 4 adult day programs and invite them to play Xbox Kinect bowling in a group setting, twice weekly for 10 weeks. We will require participants to speak and understand English, be without visual impairment, and be able to stand and walk. At pretest, participants will complete the Mini-Balance Evaluation Systems Test (Mini-BESTest) and the Montreal Cognitive Assessment (MoCA). We will video record participants during weeks 1, 5, and 10 of the intervention to capture behavioral indicators of movement confidence (eg, fluency of motion) through coding. At posttest, the Mini-BESTest and MoCA will be repeated. We will analyze quantitative data collected through the Mini-BESTest and the MoCA using an intent-to-treat analysis, with study site and number of intervention sessions attended as covariates. To analyze the videos, we will extract count and percentage data from the coded recordings.

Results: This study will address the question of whether a group motion-based technology intervention, delivered in an adult day program context, has the potential to impact balance, movement confidence, and cognitive function among people with dementia or mild cognitive impairment. The project was funded in 2019 and enrollment was completed on February 28, 2020. Data analysis is underway and the first results are expected to be submitted for publication in 2021.

Conclusions: This study will assess the feasibility and potential benefits of using motion-based technology to deliver exercise interventions to people with dementia or mild cognitive impairment. This work can also be used as the basis for developing specific software and future exercise programs using motion-based technology for people with dementia or mild cognitive impairment, as well as understanding some of the conditions in which these programs can be delivered.

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KEYWORDS

motion-based technology; dementia; mild cognitive impairment; cognitive dysfunction; postural balance; movement confidence; cognition; exercise movement techniques

Introduction

Background

Major neurocognitive disorder, also known as *dementia*, is defined as a significant decline of 2 or more standard deviations from a previous level of performance in 1 or more cognitive domains: executive function, learning and memory, complex attention, language, perceptual-motor abilities, and social cognition [1]. Causes of dementia include Alzheimer disease, cerebrovascular disease, and other conditions that affect the brain [2]. The estimated number of people living with dementia worldwide is 50 million [3], which is predicted to reach 152 million by 2050 [4].

Mild neurocognitive disorder, also known as *mild cognitive impairment* (MCI), is a common precursor to dementia, although not all people with MCI progress to dementia. MCI is characterized as cognitive decline greater than would be expected for a person's age in 1 cognitive domain that does not interfere with daily activities (eg, leisure) [1]. While MCI is not necessarily progressive, it is estimated that roughly 8.7% of people with MCI progress to dementia each year [5]. There are no pharmacological interventions to reverse cognitive changes or maintain the cognitive functioning of people with dementia or MCI [6]. As such there is an urgent need for effective interventions that support people to live well with dementia or MCI. This includes addressing physical challenges such as falls, which can undermine independence and increase the risk of hospitalization or transfer to long-term care.

People with dementia experience 2 to 8 times more falls than older people without dementia [7]. This has variously been attributed to balance impairments [8], a lack of movement confidence [9], and poor cognitive function or severity of cognitive impairment [10]. Taking balance first, people with dementia or MCI have an increased risk of developing balance impairments compared with older adults without cognitive impairment [11]. Indeed, a study involving people with subjective cognitive impairment, MCI, and Alzheimer disease found that all aspects of balance deteriorated with increasing severity of cognitive impairment [12].

Movement confidence is defined as "a person's feeling or sense of adequacy in a movement situation" [13] (pg 213). Movement confidence relies heavily on an individual's implicit belief or perception that they have the skills necessary to successfully perform a movement task [13,14]. Individuals who are movement confident are more likely to participate in movement activities to their satisfaction, whereas nonconfident individuals are less likely to participate in movement activities or find it less satisfying to participate [13,15]. This is important given that an individual's level of movement confidence relates directly to their engagement with and level of participation in physical activity and exercise [16]. Lack of movement confidence is associated with an increased risk of falling among older adults, in general [17]. Among people with dementia or MCI, lack of movement confidence is prevalent [18,19], although no studies have examined the direct link between lack of movement confidence and risk of falling. Given the above, there is a need for practical interventions that mitigate impairments in movement confidence among people with dementia or MCI. Such interventions could include physical activity and exercise, as these interventions might also impact other areas of physical function, to ensure that older people and people with dementia or MCI have the physical capacity to support the undertaking of higher-risk movements.

Exercise, independent of type (eg, cardiovascular, strength, balance and flexibility), offers a range of benefits, including decreased risk of falls, reduced risk of chronic disease, increased physical function (eg, balance), and improved cognitive function [20]. According to the Ontario Brain Institute [21], people with dementia should follow the same exercise guidelines provided by the Canadian Society for Exercise Physiology for older adults (ie, people aged ≥65 years) [22]. These guidelines recommend participation in roughly 150 minutes of moderate to vigorous physical activity per week, with moderate to vigorous physical activity deemed as activities that produce slight perspiration and a slight increase in breathing rate. It is recommended that for older adults and people with dementia moderate to vigorous physical activity consist of enjoyable activities that include cardiovascular (eg, brisk walking), strength training (eg, lifting weights), and balance exercises (eg, tai chi) [22]. The MCI practice guidelines [23] suggest that exercising twice weekly has benefits for cognition and general health. However, they do not mention the specific duration (ie, number of minutes) or type(s) of exercise to prescribe to people with MCI for optimal health benefits. However, despite the evident benefits of exercise for older people and people with dementia or MCI, only 37.3% of people aged 65 and over in Canada meet the recommended guidelines for exercise participation [24], with these numbers decreasing with advanced age and with the presence of chronic diseases, such as dementia [25]. Technology-based gaming or "exergaming" is emerging as a promising approach to overcome barriers and increase exercise participation by older adults and those with additional needs [26].

Motion-based technology (a type of exergaming technology) operates through human gestures [27]. In motion-based games, actions made in the real world (eg, reaching) are replicated by a virtual character on a screen (eg, a game character grabbing a ball). Motion-based technology has recently grown in popularity as a tool in rehabilitation and scientific research [28] with older adults [29], as well as people with Parkinson disease [30], multiple sclerosis [31], traumatic brain injury [32], and stroke [33]. For example, Pompeu and colleagues [30] showed improvements in balance among people with Parkinson disease after taking part in a 10-week motion-based technology program of 45- to 60-minute sessions 3 days per week involving a series of Nintendo Wii balance games.

A review of the use of motion-based technologies by people with dementia or MCI demonstrated that these technologies can provide enjoyable cognitive, physical, and leisure activities [27]. From a rehabilitation perspective, Schwenk and colleagues [34] showed improvements in balance and fear of falling among people with dementia or MCI after participating in a 4-week virtual reality motion-based technology program held twice weekly. Similarly, Amjad and colleagues [35] showed significant improvements in cognitive function in their participants with dementia or MCI after taking part in a 6-week motion-based technology program, held 5 times per week for 25 to 30 minutes. Moreover, when motion-based technologies are used in a group setting, they allow participants to socialize with and support one another. For example, people with dementia or MCI can play Xbox Kinect bowling "independently together" through cheering, laughing, and friendly competition [36]. Some motion-based systems have additional advantages in terms of accessibility and inclusivity, such as accommodating players who use mobility devices such as walkers and wheelchairs [37].

Objective

Despite these promising results, the impacts of interventions using motion-based technology are relatively unknown for this population. In their review of the efficacy of motion-based technology interventions for people with dementia with regard to cognition, physical function (eg, strength), emotional well-being, social health, and quality of life, van Santen and colleagues [38] identified only 3 randomized trials. We designed this study to extend knowledge of the potential of motion-based technology in rehabilitation for people with dementia or MCI. Specifically, we will examine the impacts of a group motion-based technology intervention on balance, movement confidence, and cognitive function among people with dementia or MCI. The specific hypotheses of the study reflect these aims. Hypothesis 1 states that balance will show statistically significant improvement after the motion-based technology intervention, as measured by the Mini-Balance Evaluation Systems Test (Mini-BESTest). Hypothesis 2 states that movement confidence will improve after the motion-based technology intervention, as measured by the analysis of coded video-recorded footage taken of participants during the intervention sessions (eg, number of turns completed confidently). Hypothesis 3 states that cognitive function will show statistically significant differences after the motion-based technology intervention, as measured by the Montreal Cognitive Assessment (MoCA).

Methods

Study Design

This study will use a standard within-participants design, with measurement at pre- and postintervention (1 group, 2 times).

Ethics

We received ethical approval to conduct this study from the Health Sciences Research Ethics Board at the University of Toronto (#37326) and from the University Health Network Research Ethics Board (#19-5524), Toronto, ON, Canada. Participants will be able to withdraw their consent to participate in the study at any time by informing the research team in person or using the contact information provided in the informed consent forms. We will not compensate participants for their participation in the study given that they will already be at the day program when the intervention is scheduled to take place, meaning that we do not expect travel-related costs associated with the study. If a participant injures themselves at any point during their participation in the study, we will seek medical attention immediately.

Participants

We will recruit a convenience sample of 24 people with dementia or MCI from 4 community-based adult day programs. The sample size calculation was based on detecting the minimum clinical important difference of 4.0 points [39] on the primary outcome measure (Mini-BESTest) [40], using an effect size of 0.8, an alpha value of .05, a power value of 80%, and a 2-tailed *t* test. We calculated the estimated sample size to be at least 15 participants, which we increased to 24 participants to allow for 40% attrition. We chose an attrition rate of 40% given that absenteeism and unforeseen events (eg, prolonged illness, moving to long-term care) are common among adult day program clients.

Prospective participants will be required to (1) attend the day program at least twice per week on the days in which the intervention is to be offered; (2) meet the screening criteria for the presence of cognitive impairment (determined by a score of ≤25 on the MoCA); (3) speak and understand English well enough to recognize instructions from the facilitator and respond accurately; (4) not have visual impairment that would prevent the participant to view the game screen; (5) be able to stand and walk, with or without an assistive device (eg, walker), to complete the Mini-BESTest; and (6) have the capacity to provide informed consent, or have a substitute decision maker who can provide informed consent. We will exclude participants who do not meet the above criteria from participating in the study.

Materials

Eligibility Screening Questionnaire

We will use an eligibility screening questionnaire, which we developed, to objectively record whether participants meet each item listed in the inclusion criteria. Screening questions pertain to day program schedule attendance, presence or absence of visual impairment, mobility status, presence or absence of cognitive impairment, ability to speak and understand English, and capacity to provide informed consent.

Capacity Recording Tool

We will use a capacity recording tool, along with probing questions from a pocket guide for determining a participant's decision-making capacity [41]. We will use these questions while reviewing the informed consent form to determine whether the prospective participant meets the following criteria: (1) ability to understand relevant information; (2) ability to appreciate the situation and its consequences; (3) ability to reason; and (4) ability to communicate and express a choice.

We will determine the participants who meet the 4 criteria to have the capacity to provide informed consent at that time.

Demographic Questionnaire

We will use a demographic questionnaire, which we developed, to capture participants' descriptive information, including age, sex, education level, mobility device use, current exercise participation (ie, how many days per week they engage in exercise, as well as the types of exercise they engage in), current and past (ie, within 12 months) rehabilitation service use for balance impairments (eg, physiotherapy), previous bowling experience, and previous experience using motion-based technologies.

MoCA

The MoCA is a brief assessment of global cognitive function [42]. The MoCA assesses individual domains of cognitive function, including attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. The MoCA results in scores for the individual cognitive domains that contribute to an overall total. The MoCA is scored out of 30 points, with a score of 25 points or less indicating the presence of cognitive impairment [42]. More specifically, a score of below 23 points on the MoCA indicates MCI [43] and a score of below 17 points indicates Alzheimer disease [44].

Mini-BESTest

The Mini-BESTest [40] is a 14-item comprehensive measure that simultaneously assesses several components of balance: anticipatory movements, reactive postural control, sensory orientation, and dynamic gait [45]. To complete the Mini-BESTest, participants are required to perform low-risk activities such as sit to stand, walking at different speeds, standing on a firm surface, and standing on 1 leg. The Mini-BESTest is scored out of 28 points, with higher scores indicating lesser impairments in balance [40]. While there are no prior studies using the Mini-BESTest with people with dementia or MCI, the Mini-BESTest has been shown to have excellent reliability (test-retest and interrater), internal consistency, sensitivity, responsiveness, and validity with populations similar to people with dementia or MCI, such as older adults [46], people with Parkinson disease [47], people with balance disorders [39], and people with chronic stroke [48].

Intervention Description

We will invite participants to take part in a 10-week motion-based technology intervention (Xbox Kinect bowling), held in a group setting at 4 community-based adult day programs. The intervention sessions will take place twice per week for 10 weeks (20 sessions per site). Sessions will be facilitated by the first author (ED) using teaching techniques successfully employed in previous studies involving motion-based technology and people with dementia or MCI, such as verbal prompts, gesture demonstrations, and physical assistance [37]. During each session, approximately six participants will be seated together in a room and will each have a turn to engage with the technology and game. The facilitator will call upon each participant in the group 1 at a time to take their turn, which will continue for the duration of each session (approximately 60 minutes). While the active player is engaging with the technology, the rest of the group will sit and observe.

The motion-based technology system to be used in this study is the Xbox One Kinect (Microsoft Corporation). We chose the Xbox One Kinect over other commercially available motion-based technology systems (eg, Nintendo Wii) given that interaction with this system requires no handheld controller and relies purely on naturalistic movements (eg, waving an arm). We will used the commercially available bowling game offered through the Kinect Sports Rivals package in the study, alongside the Xbox One Kinect. We chose the Kinect Sports Rivals bowling game given that the game of bowling is generally familiar.

To partake in the intervention, participants are required to rise from their chair, walk to the line (ie, a piece of black electrical tape placed on the floor in front of the technology to cue participants regarding where to stand), play the bowling game, walk back to the chair, and sit down. We will break down the movements required to play the bowling game for participants in a stepwise manner: (1) raise an arm above the head to activate the Kinect sensor; (2) reach the same arm out to the side; (3) close the hand of the extended arm to pick up a bowling ball; (4) extend the same arm back behind to wind up; (5) open the hand of the same arm to release the ball; and (6) swing the same arm forward to throw the ball.

Environment

We will hold the intervention sessions in the activity room of each adult day program site, which includes a large television set or smartboard, with enough space for participants to sit between turns and to play the game. For consistency, we will configure each day program activity room identically at each site for all intervention sessions, including the placement of the technology, the chairs, the facilitator, and the participants. The facilitator of the intervention sessions will be situated next to the game screen during all sessions to support participants as required. On the days in which video recording occurs, the video cameras will be consistently setup at the front and back of the room during the intervention to capture a comprehensive view of the active players during each of their respective turns.

Procedure

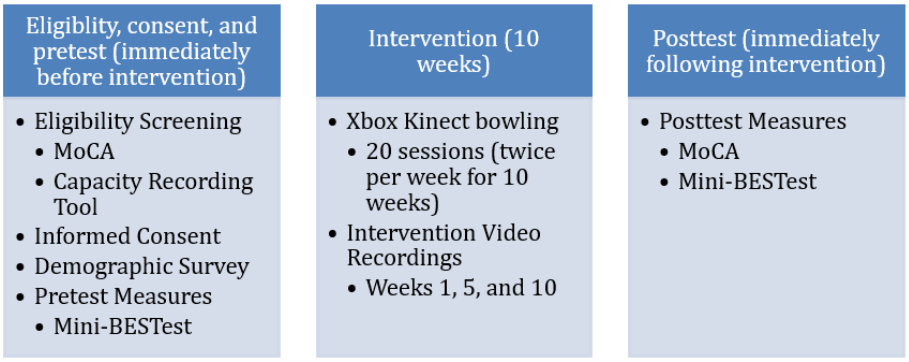
We will first ask potential participants to complete the eligibility screening questionnaire and the MoCA [42] to ensure that the study inclusion criteria are met. The MoCA will be conducted in person, in a quiet and private setting (ie, in a separate room) at each day program. The first author (ED) will be responsible for administering and scoring the MoCA. At this time, prospective participants will also rereview the informed consent with the researcher, who will then determine their capacity to provide informed consent using the decision-making ability and capacity-probing questions. Once a participant has reviewed the informed consent form to their satisfaction, they will be asked to sign the informed consent form in the presence of the researcher, provided that they have the capacity to independently provide informed consent. Given that decisions are time specific, we will review each participants' capacity to consent on an

ongoing basis (ie, at each point of interaction). All consent and assent forms will be signed in a quiet and private area at the day program.

Upon providing informed consent (whether through independent consent or substitute decision-maker consent plus participant assent), each participant will complete the demographic questionnaire and the Mini-BESTest [40]. We will complete the pretest measurements as close to the eligibility measurements and to the intervention as possible (ie, within 1-3 days) to ensure that the MoCA (used for eligibility and outcome purposes) and Mini-BESTest scores do not become outdated. We will conduct the Mini-BESTest in an open area (eg, exercise room) at each day program to ensure that there is enough space to perform the test. Additionally, 2 members of the research team will be present during the Mini-BESTest to ensure that participants can safely perform the test. That is, 1 research team member will evaluate the participants' performance while the other member acts as a spotter.

Once the pretest measures are complete, participants will take part in a 10-week motion-based technology intervention (Xbox Kinect bowling), which will be held in a group setting at each day program. Sessions will be held twice per week for 10 weeks (20 sessions), with each session lasting approximately one hour. At the start of each session, the researcher will provide all participants with a verbal and physical demonstration of how to play the game. Additionally, we will record participant attendance to track how many sessions each participant takes part in over the 10-week intervention period. During weeks 1, 5, and 10 of the 10-week intervention period, we will take video recordings of each participant during the intervention using 2 video cameras to capture physical motions related to movement confidence. Immediately following the completion of the 10-week intervention (ie, within 1-3 days), all participants will complete the posttest measures, that is, the Mini-BESTest and the MoCA, for later comparison (Figure 1).

Figure 1. Study procedure. Mini-BESTest: Mini-Balance Evaluation Systems Test; MoCA: Montreal Cognitive Assessment.



Data Analysis

Inclusion in Data Analysis

We will amalgamate data collected from all 4 adult day programs for analysis and reporting purposes. We will encourage participants to attend as many of the intervention sessions as possible; using an intent-to-treat approach, we will include all participants in the final analysis (with number of sessions as a covariate), regardless of the number of intervention sessions they attended. Participants who miss sessions will still be permitted to participate in the motion-based technology intervention. Makeup sessions for participants who are not able to attend all sessions will not be offered. Participants who miss sessions will be accounted for during the analysis.

Analysis of Test and Questionnaire Data

All analyses will follow an intent-to-treat approach, whereby we will base the results of the experiment on all participants recruited to take part in the intervention, and not just those who complete the intervention [49]. This approach to analysis will provide a more reliable estimate of the true effectiveness of the motion-based technology intervention, by reproducing what occurs in real-world settings such as community-based adult day programs. We will handle missing data using multiple imputation, which is the recommended standard for accounting for missing research data when working with people who have dementia [50]. We will include study site and the number of intervention sessions attended by the participants in the statistical model as covariates. These analyses will be conducted using IBM SPSS version 26 (IBM Corporation), using a P value of <.05 and a confidence interval of 95%.

Analysis of Video-Recorded Data

We will code video-recorded data using behavioral analysis software (Observer XT version 12.0; Noldus Information Technology) [51] to capture potential indicators of movement confidence (eg, hesitation) and how these change over time. Behavioral analysis of video-recorded data involves creating a coding scheme with operationalized definitions to objectively code the data. Coded data can capture the frequency and duration of events and behaviors, such as how often confident or nonconfident behaviors occur. This will allow for the extraction of count and percentage data related to movement confidence (eg, 20% of turns were completed confidently during week 1, which increased to 80% by week 10).

We will develop the movement confidence coding scheme using information from 2 distinct sources: (1) previous studies that examined movement confidence (eg, [13,14,16]), and (2) observations from previous work with motion-based technology and people with dementia or MCI (eg, [36,37]). For instance,

Dove and Astell [36] noted that people with dementia or MCI from an adult day program appeared to move more confidently with repeated exposure to the movement situation (ie, playing Xbox 360 Kinect bowling). That is, participants gradually transitioned from hesitant, rigid movements to relaxed, flowing movements and relied less on the instructor to complete the movement task. Indeed, over time, participants required fewer prompts (eg, verbal, gesture) and less physical support from the instructor to complete the movement task [36]. Additionally, some participants became less reliant on their mobility devices and began to develop a professional-looking bowling stance.

Video recordings will be coded by 4 independent raters, 1 of whom is the first author (ED). Prior to formally coding the videos for analysis, each rater will undergo training using the Observer XT video analysis software [51] and the movement confidence coding scheme. This will involve completing an introductory coding exercise, reviewing the video-recorded data, familiarizing themselves with the coding scheme and its operational definitions, and practicing coding the videos. We will compare the practice work of each coder for consistency using interrater reliability analysis to determine whether the 4 raters are reliably evaluating the same material [52]. This will also reduce the likelihood of researcher bias, given that the work of the other 3 raters will be compared for consistency against that of the fourth rater (ED), who is also involved in facilitating the study intervention and conducting the pretest and posttest measures. Once interrater reliability between the 4 raters reaches at least 80% agreement, the 4 raters will formally code the video recordings for analysis. This involves dividing up the coding so that each rater will be responsible for coding 1 of the 4 study sites (ie, 6 sessions per rater).

We will analyze all 6 video recordings from each data collection site. These comprise recordings of the first 2 sessions (1 and 2), the middle 2 sessions (11 and 12), and the final 2 sessions (19 and 20). Each rater will code the entirety of each selected session (60 minutes), with each bowling turn of each participant analyzed. Then, we will combine coded data from the 6 sessions into 3 respective time points: start (T1) = the first 2 sessions, midpoint (T2) = the 2 middle sessions, and end (T3) = the last 2 sessions.

Results

The motion-based technology intervention has the potential to positively impact participants' physical function, specifically balance (as measured through the Mini-BESTest) and movement confidence (analyzed from coded video recordings). This could confirm the feasibility and potential benefits of using motion-based technology to deliver exercise interventions to people with dementia or MCI. There is also potential for the motion-based technology intervention to positively impact the cognitive function of people with dementia or MCI (as measured through MoCA score), offering new approaches for cognitive rehabilitation with this population. The project was funded in 2019 and enrollment was completed on February 28, 2020. Data analysis is underway and the first results are expected to be submitted for publication in 2021.

Discussion

Principal Findings

This study is designed to examine the impacts of a group motion-based technology intervention on balance, movement confidence, and cognitive function among people with dementia or MCI. To our knowledge, this is the first study in an emerging body of literature to investigate these important outcomes with regard to the use of motion-based technology for people with dementia or MCI.

Limitations

Despite the suggested contributions of the study, the proposed study features several potential limitations. First, there is a high risk of researcher bias given that the first author (ED) will be the one to conduct all pre- and posttest measures (ie, MoCA and Mini-BESTest), facilitate the study intervention with participants, and assist with analyzing participants' movement confidence data. Thus, we recommend that future intervention studies of this nature be carried out with a larger research team where different members can be responsible for conducting different aspects of the study (ie, 1 person conducts the pre- and posttest measures, 1 person facilitates the intervention, and at least two separate individuals analyze the movement confidence data). However, from an opposite perspective, it could be considered positive that the first author (ED) was involved in all aspects of this preliminary study, in order to comment on feasibility and effectiveness, which can help to inform future studies of a similar nature.

Second, we will recruit participants via self-referral to a study advertisement, which suggests that participants who volunteer to take part in the study may be more keen to improve their balance, movement confidence, and cognitive function, which could influence their willingness to take part in the intervention.

Third, we expect that 40% of recruited participants will not complete the study intervention due to reasons outside of our control (eg, prolonged illness, moving to long-term care).

Fourth, while this study is adequately powered, the sample size is still considered small. However, small sample sizes are common in many rehabilitation studies due to lack of resources, lack of funding, recruitment challenges, and high dropout rates [53].

Fifth, the demographic questionnaire developed for this study does not capture participants' specific diagnosis (eg, Alzheimer disease) or the number of years since their diagnosis. Indeed, it cannot be ruled out that these demographic variables could impact participants' level of movement confidence, as well as their ability to improve from the intervention.

Sixth, we acknowledge that the methods being used to evaluate movement confidence (ie, analysis of coded video recordings) are pilot in nature, meaning that there is a chance that some aspects of movement confidence may not be captured using the proposed approach. We recommend that future studies also include a self-report measure or qualitative methods such as interviews, or both, to capture participants' true feeling of movement confidence.

Seventh, we will recruit a convenience sample of participants from 4 community-based adult day programs near Toronto, Canada. As such, all study participants will live in the community and come from 1 general geographical location. Thus, the findings of this study may not be generalizable to people living in different geographical locations (eg, rural and remote locations) or people living in different care settings (eg, long-term care homes). Eighth, we acknowledge that the game of bowling is not culturally inclusive and may be familiar only to people from certain cultural backgrounds (eg, North American). As a result, choosing the game of bowling may have the potential to impact the diversity of our study sample, as people who are not familiar with the game may be less likely to take part in the study.

Comparison With Prior Work

The findings of the proposed study can contribute to the literature in several regards. First, the results of this study could provide further insight into the potential impacts of motion-based technology for people with dementia or MCI, which could stimulate further outcomes-based research in this area. Second, this work can be used to inform the development and design of motion-based technology games for people with dementia or MCI. To date, commercially available motion-based technology games have not been targeted toward people with dementia or MCI, which likely plays a role in the lack of rehabilitation literature regarding the impacts of motion-based technology interventions for this population [38]. Indeed, there is a need for further research using motion-based technology systems and games that are specifically designed to be enjoyable and accessible for this population [28]. For example, systems could be developed that provide in-game prompts, thus reducing the demands on an external (eg, human) facilitator. Similarly, errorless learning capabilities among people with dementia or MCI [54] could be leveraged within motion-based technology games by creating a wider repertoire of games that can be broken down into procedural steps.

Broadly, we expect that this research will be relevant to scientific, clinical, and professional audiences. For example, we expect that this research will be relevant to scholarly rehabilitation practice, advocacy, or advancing understanding of occupation (ie, meaningful activity) as a fundamental social determinant of health and well-being for people with dementia or MCI. Understanding the potential impacts of using motion-based technology with people with dementia or MCI can inform future evidence-based, community-based rehabilitation practice. That is, if participants show significant improvements in balance, movement confidence, and cognitive function as a result of partaking in the motion-based technology intervention, there is the potential of motion-based technology systems being incorporated into rehabilitation interventions targeting these outcomes. Additionally, we expect that this study will demonstrate the feasibility of using motion-based technology to deliver task-specific interventions to people with dementia or MCI. This is relevant given that tasks and goals of importance to clients are often used to inform rehabilitation interventions. Finally, this research aims to advocate the inclusion of people with dementia or MCI in rehabilitation science and interventions. We expect that this study will demonstrate the ability of people with dementia or MCI to engage in meaningful activity and emphasize the importance of meaningful activity to support health and well-being of people with dementia or MCI.

Conclusions

The purpose of the proposed study is to examine the impacts of a group motion-based technology intervention on balance, movement confidence, and cognitive function among people with dementia or MCI. The findings of this study could confirm the feasibility and potential benefits of using motion-based technology to concurrently deliver cognitive and physical interventions to people with dementia or MCI. Confirming the feasibility of potential benefits of using motion-based technology with people with dementia or MCI could have several implications for research, clinical practice, and recreational care targeting this population.

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Conflicts of Interest

None declared.

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Abbreviations

MCI: mild cognitive impairment
Mini-BESTest: Mini-Balance Evaluation Systems Test
MoCA: Montreal Cognitive Assessment

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Protocol

Assessing the Effectiveness of Policies Relating to Breastfeeding Promotion, Protection, and Support in Southeast Asia: Protocol for a Mixed Methods Study

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Abstract

Background: Despite its well-known benefits, breastfeeding practices remain suboptimal worldwide, including in Southeast Asia. Many countries in the region have thus enacted policies, such as maternity protection and the World Health Assembly International Code of Marketing of Breast-milk Substitutes (the Code), that protect, promote, and support breastfeeding. Yet the impact of such national legislation on breastfeeding practices is not well understood.

Objective: This study aims to review the content, implementation, and potential impact of policies relating to maternity protection and the Code in Myanmar, the Philippines, Thailand, and Vietnam.

Methods: This mixed methods study includes a desk review, trend and secondary data analyses, and quantitative and qualitative data collection. Desk reviews will examine and compare the contents, implementation strategies, coverage, monitoring, and enforcement of national policies focusing on maternity protection and the Code in each country with global standards. Trend and secondary data analyses will examine the potential impact of these policies on relevant variables such as breast milk substitute (BMS) sales and women's workforce participation. Quantitative data collection and analysis will be conducted to examine relevant stakeholders' and beneficiaries' perceptions about these policies. In each country, we will conduct up to 24 in-depth interviews (IDI) with stakeholders at national and provincial levels and 12 employers or 12 health workers. Per country, we will survey approximately 930 women who are pregnant or have a child aged 0-11 months, of whom approximately 36 will be invited for an IDI; 12 partners of the interviewed mothers or fathers of children from 0-11 months will also be interviewed.

Results: This study, funded in June 2018, was approved by the Institutional Review Boards of the relevant organizations (FHI 360: April 16, 2019 and May 18, 2020; and Hanoi University of Public Health: December 6, 2019). The dates of data collection are as follows: Vietnam: November and December 2019, May and June 2020; the Philippines: projected August 2020; Myanmar and Thailand: pending based on permissions and funding. Results are expected to be published in January 2021. As of July 2020, we had enrolled 1150 participants. We will present a comparison of key contents of the policies across countries and against international standards and recommendations and a comparison of implementation strategies, coverage, monitoring, and enforcement across countries. We will also present findings from secondary data and trend data analyses to propose the potential impact of a new or amended policy. For the surveys with women, we will present associations between exposure to maternity protection or BMS promotion on infant and young child feeding practices and their determinants. Findings from IDIs will highlight relevant stakeholders' and beneficiaries' perceptions.

Conclusions: This study will increase the understanding of the effectiveness of policy interventions to improve breastfeeding, which will be used to advocate for stronger policy adoption and enforcement in study countries and beyond.

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KEYWORDS

breastfeeding; breast milk substitute; Code of Marketing of Breast-milk Substitutes (The Code); maternity protection; maternal, infant, and young child nutrition; mixed methods study; Southeast Asia

Introduction

Breastfeeding Benefits and Determinants

The benefits of breastfeeding for child survival, health, and development as well as maternal health and wellbeing have been well-documented in low-income, middle-income, and high-income countries [1]. By improving breastfeeding rates, an estimated 595,379 deaths due to diarrhea and pneumonia among children 6-59 months of age and 98,243 maternal deaths due to breast and ovarian cancer and type 2 diabetes, along with 974,956 cases of childhood obesity, could be prevented annually [2]. In addition to being better protected against infectious diseases and overweight and obesity, children who have been breastfed are at reduced risk for type 2 diabetes [3], perform better on intelligence tests [3], have higher educational attainment [4], and have higher adult earnings [5]. Women who have breastfed are more likely to maintain a healthy body weight [6,7] and less likely to suffer from depression [8]. Given the benefits of breastfeeding, the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) recommend that mothers start breastfeeding their babies within the first hour of life and exclusively for the first 6 months and continue to breastfeed along with appropriate complementary feeding up to 2 years of age and beyond [9]. Breastfeeding generates significant economic gains for households, communities, and countries. Analysis by the World Bank suggests that every dollar invested in breastfeeding generates US $35 in economic returns [10]. Globally, the total economic losses due to health system treatment costs, premature mortality, and cognitive losses are estimated to be US $341.3 billion per year or about 0.7% of global gross national income [2].

Despite all that is known about the benefits of breastfeeding, breastfeeding practices remain suboptimal worldwide [1,11]. Although nearly all women are biologically capable of breastfeeding, the decision to breastfeed is influenced by a variety of societal, community, household, and individual factors [11]. According to Rollins et al [11], breastfeeding is determined by factors at structural or societal levels in different settings like the health system, workplace, and community and at the individual level. Within the health care system, providers strongly influence feeding decisions during the period before, during, and after birth and are the most likely sources of support when challenges occur [12,13]. The extent to which health care providers are equipped to deal with breastfeeding challenges can impact breastfeeding practices [1,11]. Family and community are also important sources of breastfeeding support at the interpersonal level, and women whose partners support breastfeeding breastfeed longer [14,15]. On an individual level, a mother's decision to breastfeed is influenced by the advice and support she receives, her confidence and self-efficacy to breastfeed, as well as positioning and attachment [16-19].

Breastfeeding is also influenced at the structural level, such as by policies that can support, protect, or promote the practice, including maternity protection and the international code on the marketing of breast milk substitutes (BMS).

Maternity Protection

Across the globe, a mother's return to work after childbirth is one of the primary reasons for not breastfeeding or for early cessation of breastfeeding [20]. Increasing the duration of paid maternity leave has been shown to be an effective intervention for improving breastfeeding rates. Recent analysis of trend data from 38 low-income and middle-income countries illustrates that increasing the duration of paid maternity leave is associated with a significantly higher prevalence of early initiation of breastfeeding, exclusive breastfeeding among infants <6 months old, and longer duration of breastfeeding [21]. Mothers can continue breastfeeding after returning to work if maternity leave or childcare is available and if breastfeeding or the expressing of breast milk is supported [22]. Multiple studies have shown that providing working mothers with time, space, and support for breastfeeding when they return to work can increase breastfeeding duration and adherence to recommended breastfeeding practices [23-25].

The International Labor Organization (ILO) Maternity Protection Convention, 2000 (No. 183) [26] and its accompanying Recommendation (No. 191) [27] call for the establishment of an integrated set of essential measures to help initiate, establish, and maintain optimal breastfeeding practices: (1) maternity leave for at least 14 weeks with full pay; (2) prenatal, childbirth, and postnatal health care for both the mother and her child and cash benefits for women who do not qualify for social insurance; (3) protection for a pregnant or nursing worker from engaging in work that could be detrimental to her health or that of her child; (4) the right to return to the same or similar paid position at the same salary rate; (5) protection from discrimination at work; and (6) the right to one or more daily breaks or a reduction in working time. Compliance and commitment to the ILO Convention vary significantly by country [26,28], with nearly 50% of countries not meeting the minimum 14 weeks (Conventions 183) and less than 25% meeting the convention No. 191 of 18 weeks or more. The sources of funding for maternity entitlements also vary from public financing, employers, employee contributions, and a mix of these [28]. Some policies provide support to women after returning to work, while others do not [28]. To effectively

advocate for appropriate maternity protection policies, it is necessary to study the impact of existing policies as well as perceptions of maternity protection among employees, employers, and policy makers.

World Health Assembly International Code of Marketing of Breast-Milk Substitutes

Breastfeeding is also affected by the aggressive marketing and widespread availability of BMS. Such marketing can influence social norms in favor of BMS and undermine mothers' confidence to breastfeed, resulting in suboptimal breastfeeding practices [29]. To limit inappropriate marketing practices and the harmful effects of marketing of BMS, feeding bottles, and teats, the World Health Assembly (WHA) adopted the International Code of Marketing of Breast-milk Substitutes (referred to as the Code) [30] and subsequent WHA resolutions.

As of April 2020, 136 of 194 (70%) WHO member states have implemented legal measures related to the Code. Of these, only 25 countries have measures "substantially aligned" with the Code based on a WHO/UNICEF/ International Baby Food Action Network checklist of provisions of the Code and relevant WHA resolutions [31]. Further, although for legal measures to be effective they must include clear provisions enabling authorized agencies to take corrective action when Code violations are identified, only 73 (73/194, 38%) countries clearly identify which government agencies are responsible for monitoring compliance, and only 82 (82/194, 42%) countries define sanctions for violations [31].

Although there is evidence of the negative impact of the provision of free BMS samples or promotion through trusted health workers [32,33], there has been little exploration of how national policies on the Code have impacted breastfeeding. Similarly, no studies have directly evaluated the impact of the Code on marketing and promotion practices, exposure to advertising, attitudes towards BMS and breastfeeding, and BMS sales [29].

Study Goal and Objectives

The goal of this study is to determine the impact of breastfeeding-related policies in Myanmar, the Philippines, Thailand, and Vietnam. To do so, researchers will review the content, implementation, and potential impact of policies relating to breastfeeding promotion, protection, and support in these countries; however, depending on the local context, the study in each country will examine key policies related to maternity protection and the Code.

Specific study objectives are to (1) review the content of national policies on maternity protection and the Code; (2) review the implementation, coverage, monitoring, and enforcement of these policies across countries; (3) examine the potential impact of these policies on relevant outcomes (eg, for maternity protection, impact on workforce participation by women; for the Code, impact on exposure to BMS marketing); and (4) examine perceptions of relevant stakeholders and beneficiaries (eg, pregnant and lactating women) about these policies (eg, perceived benefits, limitations, difficulties, areas for improvement, recommendations).

Methods

Study Setting

The study will be conducted in Myanmar, the Philippines, Thailand, and Vietnam. In recent years, each of these countries has made a significant policy change related to maternity protection or the Code.

Myanmar

Working mothers in Myanmar are entitled to 14 weeks of paid maternity leave (18 weeks for twins) in the private sector under the Social Security Law (2012) and the Leave and Holidays Act (1951, amended 2014) [34]. Mothers working in the public sector are entitled to 6 months paid maternity leave according to the revised Handbook of Civil Servant Rights (2013) [34]. Employers are required to pay a woman's wages while she is on maternity leave, regardless of whether she is enrolled in the social security system. Women who are enrolled in the social security system are entitled to additional cash and noncash benefits during pregnancy and after delivery. According to the Factories Act (1951, amended 2016), in factories where more than 100 female workers are employed, employers must set up and maintain a childcare room [34]. There is no legislation that addresses nursing breaks at work.

In 2014, Myanmar's Food and Drug Board of Authority issued the Order of Marketing of Formulated Food for Infant and Young Child under the National Food Law, which regulates the marketing and labeling of BMS, complementary foods, and bottles and teats intended for children under 2 years of age.

The Philippines

In the Philippines, working mothers are entitled to 9 weeks of paid maternity leave, all of which is funded by social security [28]. Since 2018, the Republic Act has provided more supportive policies, including increasing the maternity leave period to 105 days for female workers with an option to extend for an additional 30 days without pay and granting an additional 15 days for solo mothers. This substantially increased the previous entitlement of 9 weeks and covers public, private, and informal sector workers. The Expanded Breastfeeding Promotion Act (2009) of the Philippines provides that expenses for establishing lactation stations are tax-deductible. The Department of Labor and Employment issued a policy to guide the establishment of lactation stations in varied workplace settings and have included these spaces in the monitoring of labor law compliance of private enterprises.

The Philippines was among the first countries to pass national legislation on the Code in 1986. In 2006, the Implementing Rules and Regulations of the Code were revised to align with international standards and were approved [35]. Executive Order 51 covers infant formula, follow-up formula, feeding bottles and teats, and other related products, but not complementary foods or milk for mothers. While monitoring of the Code and its Implementing Rules and Regulations resulted in the processing of 24 alleged violations between 2011 and 2012 [36], monitoring and enforcement at national and subnational levels remain a challenge. In 2018, a new **Republic Act** revised

the definition of BMS by law to include any type of milk marketed for feeding of infants aged up to 36 months.

Thailand

Thailand has not yet ratified ILO Convention 183, which provides maternity protection. In 1990, Thailand approved the Social Security Act B.E 2553 entitling mothers to 90 days of maternity leave. During maternity leave, 50% of the salary is paid by the employer for 45 days, and 50% is paid by social security for 90 days. To be eligible for social security payments, the insured person must have paid contributions for at least 7 months during the 15 months prior to the date of receiving medical benefits. Currently, there is no mention of breastfeeding breaks in the Thai law.

In 2017, the National Legislative Assembly passed the Marketing Control on Food for Infants and Young Children Act to restrict the marketing of food for infants and young children. Under the revised legislation, the government of Thailand prohibits all marketing of BMS for children under 12 months of age, with further regulations that apply to marketing of similar products to children under 3 years of age.

Vietnam

The National Assembly extended paid maternity leave from 4 to 6 months, effective from 2013. Working mothers in Vietnam are also entitled to paid nursing breaks (up to 60 minutes) by law, for up to 12 months [28]. The funding is from the social security fund.

In 2012, the National Assembly voted in favor of implementing a total ban on the promotion of BMS for children up to 2 years of age. The government guiding decree on marketing and use of feeding products for young children, feeding bottles, teats, and pacifiers was approved in 2014 [37].

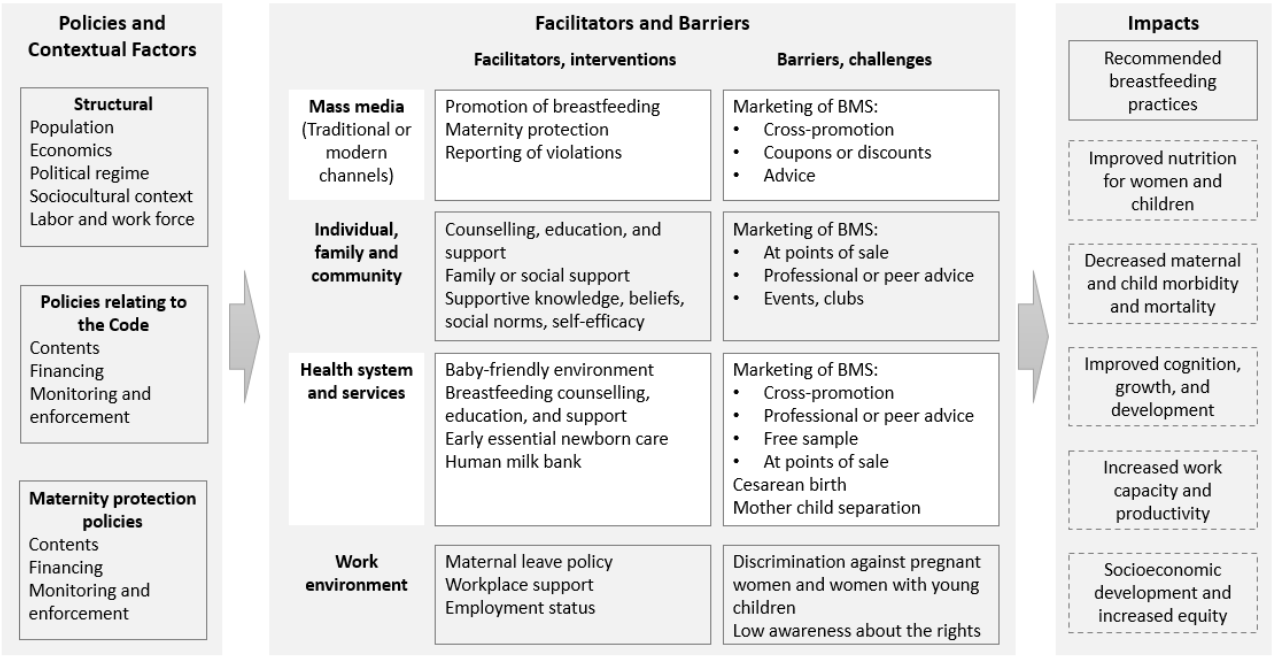
Study Design and Methods

This is a mixed-methods study, employing desk reviews, secondary data analysis, and primary quantitative and qualitative data collection (Figure 1). Our study was designed using a conceptual framework (Figure 2) that was developed based on previous literature [11,38-46].

Figure 1. Methods for each study objective.

Objectives	Desk reviews	Secondary data analysis	In-depth interview	Surveys
1. Review the content of national policies on maternity protection and the Code	√			
2. Review implementation, coverage, monitoring, and enforcement of these policies across countries	√		√	
3. Examine the potential impact of these policies on relevant outcomes		√		√
4. Examine perceptions of relevant stakeholders and beneficiaries about these policies			√	

Figure 2. Conceptual model. The dashed lines indicate content not measured in the study. BMS: breast milk substitute.



Desk Review Policy Content and Implementation

For each country, we will collect and review relevant maternity protection and the Code policies. These will be collected through government websites (eg, Parliament, Ministry of Health) and other official sources. Key informants, consultants, or country staff will help to identify and collect documents not publicly available. Researchers will extract key information from the collected documents using a semiquantitative policy data extraction form (Multimedia Appendix 1). Two researchers will review each policy, compare the results, and discuss the differences before creating the final form. The extracted information will then be compared to international standards (eg, the Code and subsequent WHA resolutions and ILO Maternity Protection Convention 2000 [No. 183] [26] and Maternity Protection Recommendation 2000 [No. 191] [27]).

We will review the implementation, coverage, monitoring, and enforcement of relevant policies focusing on maternity protection and the Code. Key informants, consultants, or country staff will help to identify and collect documents and data related to the number and proportion of working mothers receiving maternity benefits, details of monitoring and reporting activities, as well as the number of the Code violations and penalties enforced.

Secondary Data Analysis

Secondary data will be drawn from national maternal, infant, and young child nutrition and health surveys, such as Multiple Indicator Cluster Surveys (MICS), Demographic and Health Surveys (DHS), or labor force surveys. Because the availability of secondary data sets and trends may vary across countries, we will identify all relevant data (eg, based on reviewing survey questionnaires, codebook, and reports) and secure access via locally contracted research firms. Univariate, bivariate, and multivariate data analysis will be used to analyze individual-level data.

We will analyze data using an interrupted time-series approach to quantify the change in the slope or level of selected outcomes before and after the implementation of a policy [47]. For maternity protection, the trend data could be the number of women participating in the workforce, recipients, and expenditures that might be accessed and used. For the Code, trend data will be advertising occurrence and expenditure of BMS companies by product and channel (obtained through media agencies or a rapid media audit) and sales of BMS by BMS type (purchased from Euromonitor [48]). The research team has successfully used interrupted time-series analysis in a prior publication [49].

Primary Qualitative and Quantitative Data Collection

We will conduct in-depth interviews (IDIs) with stakeholders, including policy makers or authorities at national and subnational levels; staff of the United Nations, nongovernmental organizations (NGOs), research organizations, and media; and employers and health workers (Table 1). Participants must meet the following eligibility criteria: be at least 18 years of age; willing to participate in the study; and have knowledge, a role, or a responsibility relating to the maternity protection policies or the Code.

Table 1. Study participants, research methods, and sample size per country.

Participant group	In-depth interview, n (per country)	Quantitative survey, n (per country)
National level		
Policy makers or authorities	7	N/A[a]
Stakeholders from the United Nations, nongovernmental organizations, research organizations, media	7	N/A
Subnational levels (state, region, or province)		
Policy makers or authorities	10	N/A
Employers (study with maternity protection component)	12	N/A
Health workers (study with the Code component)	12	N/A
Women		
Pregnant	12	310
Mothers with children aged 0-5 months	12	310
Mothers with children aged 6-11 months	12	310
Partners of the interviewed mothers with children aged 0-11 months	12	N/A
Total sample size	Up to 96	930

[a]N/A: not applicable.

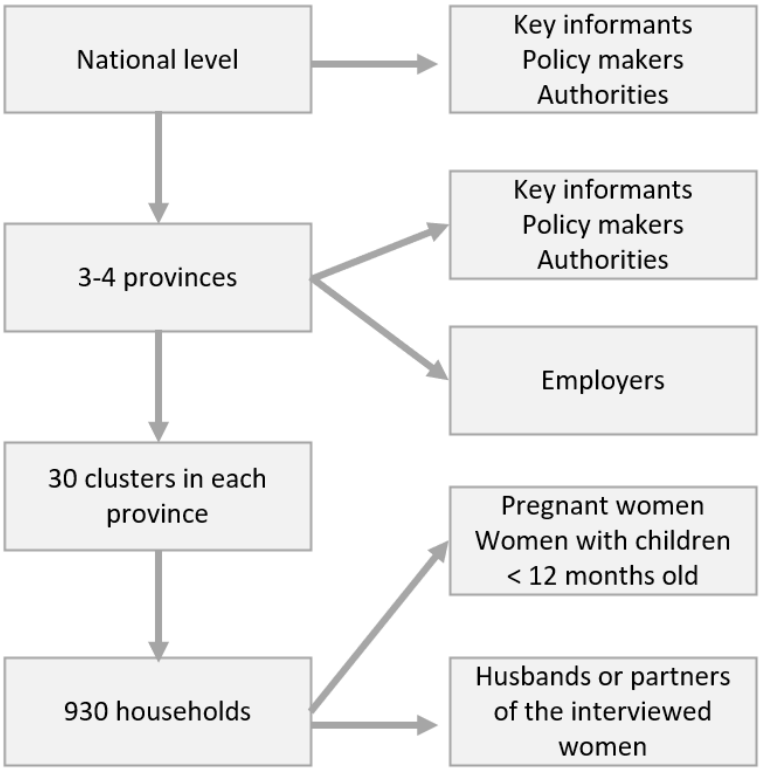
We will also collect primary data from pregnant women and mothers with children aged 0-11 months using IDI guides and structured questionnaires; we will collect data from these women's partners using IDI guides (Table 1). These participants must also be at least 18 years of age and willing to participate in the study.

The sample size for IDIs is based on information saturation. If saturation is achieved sooner, fewer IDIs will be conducted, while if saturation is not achieved, the sample will be expanded [50].

The sample size for the quantitative survey of women was determined by using the simple sampling equation with some adjustment for the design effect [51]. We chose this equation because we seek descriptive information from each group of women in each country, without comparing before and after or across groups. The quantitative sample size is based on an estimated *P* of 50% (largest sample size), confidence level of 95%, absolute precision of 7%, and design effect of 1.5. In each country, the minimum sample size is 310 women for each of the 3 following groups: pregnant women, mothers of children aged 0-5 months, and mothers of children aged 6-11 months. Thus, in each country, we will interview 930 women divided equally across the selected provinces.

Primary data collection will be conducted at the national, provincial, and community levels (Figure 3). For the quantitative survey in each country, we will use a stratified multistage random sampling procedure, where stratification will be by province, and communities will be selected in the first stage of sampling.

Figure 3. Sampling procedure.



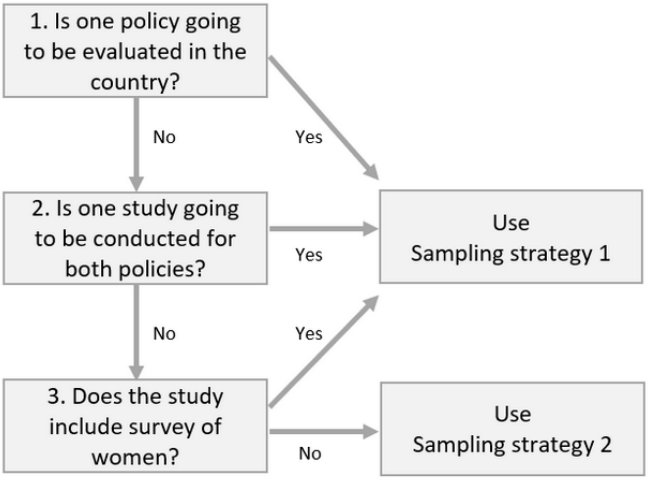
The identification of key informants at the national level will start with member lists of working groups and committees related to food, nutrition, consumer protection, and labor. Key informants for the study of the Code will include representatives from the Ministry of Health, Ministry of Trade, UNICEF, and WHO, among others. Key informants for the study of maternity protection policies include those from the Ministry of Labor, Social Insurance, ILO, UNICEF, and WHO, among others. The key informants will help to identify other potential participants from NGOs, research institutions, and media at the national level.

At the provincial level, research firms will identify a potential list of provinces in which to conduct the study with the support from national key informants and the Alive & Thrive team. The selection of provinces will largely be based on feasibility considerations. The primary criteria are urban provinces or provinces with industrial zones with female workers and research firms that have good connections and working relationships in these provinces. Provinces will be excluded if they are deemed not feasible or inefficient for study conduct, such as remote provinces with low population density or those that are not safe for the research teams. Provinces that generate income mainly from the agricultural or self-employed sectors will not be included because of the lower chance of obtaining a sufficient sample size of formally employed women. In each country, from the list of eligible provinces, the research firm will purposively select 3-4 provinces to improve capture variation by region. We acknowledge that with this sampling strategy, generalizability of the findings will be limited to the selected provinces.

The research firm will contact potential participants by phone to explain the purpose, requirements, and logistics of the survey, and the firm will follow-up with an official letter. The next step entails a kickoff meeting at the provincial level to develop a detailed list of potential participants. The provincial key informants will introduce the research firm and help to schedule an appropriate time and place for the interview. Informed consent will be obtained by interviewers before the IDI. If the appointment is missed, researchers will be allowed to reschedule up to 2 times.

At the community level, for each country, researchers will choose which policy(ies) to evaluate and if the study will include both maternity protection and the Code. This decision will be based on each country's situation and need, availability of funding, and the capacity of the research firm. The community-level sampling strategy relies on this decision (Figure 4). Specifically, if a study includes survey of women, we will use sampling strategy 1, while if a study includes only IDI, we will use sampling strategy 2.

Figure 4. Decision tree for the selection of sampling strategies for women and partners in each province.



For sampling strategy 1 (with a survey of women), from each of the selected provinces, we will employ a multiple-stage cluster sampling design in each province. Stage 1 is the selection of districts. We will select 3-4 districts in each province using a simple random selection technique. Stage 2 is the selection of clusters and primary sampling units (PSUs). We will define a sample frame of clusters and use the probability-proportional-to-the-size cluster sampling technique to select 30 clusters in the selected districts. A cluster will be a next lower level of subdistricts, which could be communities, villages, or population groups depending on the country context. The proposed minimum number of mothers of children in each PSU is about 1.5 to 2 times the sample size needed in each PSU to ensure we have a sufficient number of participants. Stage 3 is the selection of participants. We will select pregnant women and mothers of children aged 0-5 and 6-11 months in each cluster using systematic random sampling. In selected clusters, 3 lists of potential participants will be created: (1) pregnant women, (2) mothers of children aged 0-5 months, and (3) mothers of children aged 6-11 months. Based on the list and required sample size in each cluster, a list of potential participants will be selected using systematic random sampling.

Based on the list of potential participants, the community representative will call the potential participants to invite them to participate in the study. If they agree to participate, the community representative will introduce participants to the study representative in person and leave the interviewer with the participant. During the interview, the interviewer will introduce himself or herself as well as the purpose of the study, obtain informed consent, and conduct the interview. The interview will be conducted in a quiet, private location that is neither a health facility nor workplace to minimize the participants' risk of exposure or discomfort. Three attempts to visit the household will be made to complete the interviews with selected and eligible participants. If the interviewers could not meet the participants after 3 attempts, the participants will be replaced with one in the pre-identified list.

A subset of women surveyed will be invited for an IDI. Also, a subset of partners of mothers with children 0-11 months old will be invited to participate in an IDI. After completing the interview using the structured questionnaire, the interviewers will propose women or partners for an IDI, and the team leader will make the final decision of whom to invite for an IDI. The selection of women or their partners for an IDI will be based on the potential for increasing our understanding of how policies impact breastfeeding practices and collecting case studies. For example, IDIs with women will be conducted among those who (1) went back to work before completing maternity leave or completed maternity leave entitlement before returning to work, (2) weaned her child before or upon return to work or continued breastfeeding after returning to work, (3) experienced discrimination at work due to her pregnancy or birth or did not experience discrimination, or (4) knew the benefit of breastfeeding but stopped breastfeeding early and used infant formula or continued breastfeeding and did not use infant formula.

Sampling strategy 2 is for an IDI-only evaluation study (no survey of women). In each country, we will conduct IDIs with 12 pregnant women, 24 mothers of children aged 0-11 months, and 12 fathers of children aged 0-11 months (Table 1). In each of the 3-4 selected provinces, we will select 2-3 districts and 1 subdistrict from each district. Prior to the research team traveling to the field, they will share the eligibility criteria with a pre-identified community representative. In addition to the general eligibility criteria, we will seek women and partners of women who (1) went back to work before completing maternity leave or completed maternity leave entitlement before returning to work, (2) weaned her child before or upon return to work or continued breastfeeding after returning to work, or (3) experienced discrimination at work due to her pregnancy or birth or did not experience discrimination. The community representative will contact potential participants meeting the criteria to invite them to participate in the study. The community representative will make a list of those who agree to participate and schedule the day and time of the interview. The procedure for conducting the interview will be the same as in sampling strategy 1.

Study Contents and Variables

Regarding the qualitative components, IDI domains are summarized in Figure 5 for each group of participants. The IDI guides were developed based on study objectives and research questions. Complete IDI guides are in Multimedia Appendix 2.

Using projective techniques, interviews entail asking participants questions about images they are shown that relate to the study questions. These images will be adapted to each country context. Multimedia Appendix 3 has images designed to facilitate IDIs in Vietnam.

Figure 5. Domains of the in-depth interviews by study participant type.

Domains	Stakeholders	Employers or health workers	Women with child aged 0-11 months	Partners of the women with a child aged 0-11 months
Policy(ies) development	√			
Policy(ies) implementation	√	√		
Policy(ies) monitoring and enforcement	√	√		
Perceptions of and experience with policy(ies)	√	√	√	√
Suggestions for improvement	√	√	√	√
Sharing responsibilities caring for children and domestic tasks			√	√

IDIs with key informants will explore implementation, monitoring, and enforcement of the policies; bottlenecks for implementation; and proposed solutions. IDIs with employers will explore their perceptions about the benefits and disadvantages of the policies for businesses and employees.

The purpose of the IDIs with pregnant women and mothers of children aged 0-11 months is to gain deeper insight into respondents' understanding and perceptions of policies related to maternity protection and the Code including perceived benefits and challenges as they relate to study outcomes (at individual, family, employer, society levels) such as challenges of continuing breastfeeding when returning to work, benefits of maternity protection policies on continued breastfeeding, and changes in breastfeeding practices due to exposure to BMS products.

The purpose of the IDIs with partners of the interviewed pregnant women and mothers of children aged 0-11 months is to learn about respondents' understanding and perceptions of policies related to maternity protection and the Code as well as paternity leave and the role of partners in taking care of children and in domestic tasks.

For the quantitative survey, we adapted questionnaires from other studies such as NetCode [52], ILO Maternity Protection [28], MICS [53], checklists and questionnaires for early essential newborn care [54,55], and a study by Alive & Thrive on the impact of interpersonal and mass media on breastfeeding practices and an online assessment on the perception of employed women on maternity protection [56-58].

We developed separate questionnaires for pregnant women (Multimedia Appendix 4) and women with children aged 0-11 months (Multimedia Appendix 5) with quite similar contents and structures. The 6 main sections are (1) background information, (2) perinatal care, (3) behavioral determinants (intentions, knowledge, beliefs, social norms, and self-efficacy), (4) media exposure and participation in social group and events, 5) exposure to BMS promotion, and (6) maternity protection (only asked of formally employed women). The questionnaire for women with a child aged 0-11 months has additional information related to the child's characteristics, delivery, and postnatal care and the benefit of maternity protection received after birth (duration of paid leave, cash and medical benefits, work protection, breastfeeding upon return to work).

We pretested the data collection tools. IDI guides and survey questionnaires were initially developed in English and will be translated into each country's official language. Another translator will back-translate questionnaires into English to ensure that the content and spirit of the original questions are maintained. Data collection tools will be pretested in face-to-face interviews with at least 2 pregnant women, 2 mothers with children aged 0-11 months (using survey questionnaire and IDI guides), and 2 fathers of children aged 0-11 months (using IDI guides). IDI guides for other participants will be reviewed by an external experienced researcher. Necessary modifications will be made based on feedback from pretesting

Data Collection

Data Collection Team Formation and Training

Data collection teams formed by local research firms will be responsible for data collection. Each team will include one field supervisor and interviewers. Research firms will identify potential interviewers from a pool of candidates and select interviewers by screening curriculum vitae and conducting interviews.

Before data collection, the principal investigator (PI) of the research firms and the FHI 360 PI will train all interviewers and field supervisors for 4 days on the purpose of the study, terminology, concepts, data collection methods, tool pretesting, and reflection. The training will cover skills, including interview techniques, confidentiality, and privacy, as well as afford the study team the opportunity to practice administering the questionnaires and IDI guides. The training will ensure all interviewers and field supervisors understand the procedures and follow the standardized guidelines to guarantee data quality.

Informed Consent

A trained interviewer will explain the research study in detail, including the study objective and potential risks and benefits of participation, and obtain oral informed consent from the participants before any study procedures are performed (Multimedia Appendix 6). The consent form will then be signed by the researcher. Except for interviews using phone or mobile apps, the informed consent form will be printed and given to potential research participants. Interviews may be conducted by phone or mobile apps with national stakeholders. In this case, interviewers will share the informed consent form (eg, by email, shared screen) and obtain a digital signature before conducting the interview. All paper-based signed consent forms will be kept securely in a locked metal box in the study vehicle — separate from any interview notes or other study documents — and, once transferred to the firm's main office, will be kept in a locked cabinet with limited access and then will be transferred to Alive & Thrive's Southeast Asia Office (Hanoi, Vietnam).

Personal Identification Number (PIN)

After the informed consent process, participants will be assigned a personal identification number (PIN), which will be used to link all data collected from an individual in each of the research steps. The PIN is not linked with any information that would identify an individual participant. At the household level, the PIN will be first assigned to the woman participating in the survey. If she is selected for an IDI, her PIN will be unchanged. If her partner participates in an IDI, his PIN will be P (for partner) plus the PIN of the woman. This approach will help to link information of the survey questionnaire with the IDI with the women as well as to link information of a surveyed woman with her partner.

Interview Conduct

Trained interviewers will conduct the IDIs. We will audio record the interviews (with participant consent). For participants who do not consent to audio recording, the interviewers will take detailed notes during the interview.

For the quantitative survey of women, a computerized-assisted survey instrument will be used. The questionnaire will be set up in a web-based application and run on an Android tablet. The interviewer must ensure the completeness and logical flow of the questionnaire before leaving the household.

At the end of the quantitative interview, if the interviewer finds the woman suitable for an IDI (using criteria shared during the data collector training), he or she will ask if the woman is willing to participate in an IDI. If the woman agrees, the interviewer will ask for a contact telephone number as well as set a tentative date, time, and location for the IDI. After receiving confirmation from the coordinator at the central level, the qualitative interviewer will schedule the IDI.

To facilitate quality assurance (eg, random checks of questionnaires to assess completeness and consistency), at the end of the quantitative interview, the interviewer will ask for the telephone number of the participant. Before asking for the telephone number, the interviewer will confirm that the telephone number will only be used to contact the woman in a rare case when the research team needs to clarify certain information provided or to ask about her interview experience. The interviewer will emphasize that providing the telephone number is optional.

Data Management

IDI Data

The name of audio files collected during IDIs will be linked with the respondent's PIN. After each day, the audio files will be uploaded to password-protected computers and a secure cloud account. Research assistants from the research firm will transcribe the tapes in the local language. The analytical memos for IDIs will be translated to English to support the report writing. At a later stage, the transcriptions and notes will be translated into English for further analysis. The completed text files will be input to Microsoft Word files and uploaded to NVivo for further analysis.

Quantitative Survey Data

Qualitative data will be collected and managed using a digital approach. The questionnaire will be converted to a digital data collection form (eg, Open Data Kit). A data management system will be developed in each country by the local research firm and validated by the FHI 360 staff to ensure that data are fit for analysis purposes.

During data collection, interviewers will enter the information directly into a password-protected tablet. When connected to the internet, data will be synchronized to a secure server of the platform provider (eg, Open Data Kit). Synchronization will be done at least once per day. After uploading, the data will be deleted from the tablets. Two back-up tablets will be provided to each data collection team.

In very rare cases when data collection could not be done using tablets, a paper questionnaire will be used. The interviewer will review the questionnaire for completeness before ending the interview. The supervisor will then review and approve the questionnaire. Completed questionnaires will be entered into the tablet within 24 hours in the field, with a note about why the tablet was not used during the interview. The completed paper questionnaires (if any), consent forms, and other study documents will be stored in a locked box in the vehicle during transportation and in the hotel room at night.

Supervisors at the central level will access data from the cloud, perform data checks and cleaning, and provide feedback about data quality to data collection teams within a day. This will identify and address any issues relating to the questionnaire and data collection in a timely manner.

Raw data will be submitted to Alive & Thrive immediately following the end of data collection. An assigned researcher or research assistant will perform required data management (eg, creating indicators from collected variables) prior to data analysis. Any changes in the dataset will be done through program syntaxes to allow for cross-checking and to ensure that findings are reproducible. Corresponding justifications and individuals who approve each change will be documented.

Data Analysis

Primary Quantitative Data Analysis

For maternity protection, we will analyze associations between exposure to maternity protection (eg, taking leave, duration of leave, paid leave, lactation support at work, social norms) and infant and young child feeding practices. For the Code, we will analyze associations between exposure to BMS (eg, advertisement, advice, gift) and infant and young child feeding practices as well as women's intentions, knowledge, beliefs, social norms, and self-efficacy.

Some data will complement the IDI with women related to perceptions of the maternity protection legislation and the Code. Each estimate will be accompanied by 95% CIs, and the cluster design effect (eg, by PSU) will be accounted for by using complex survey data analysis methods or with the robust option. Sampling weights as appropriate for each stratum (eg, province, woman group) will be calculated and used when combining data from different strata, for example for the overall country-level analysis. For overall and country-specific data analyses, we will use Stata version 15 (StataCorp LLC, College Station, TX).

Primary Qualitative Data Analysis

IDI content will be transcribed and analyzed. Transcripts will be produced using notes taken and recorded audio files. The full transcripts, written in the local language, will be analyzed by in-country research teams. Depending on the availability of a data platform, the analysis will be done in NVivo (or a similar program) or by color-coding the text. The transcripts will then be translated into English for further analysis by FHI 360 or Alive & Thrive staff or consultants to facilitate comparison across countries using NVivo.

The main steps will comprise codebook development, double-coding of a sample of transcripts with intercoder agreement checks, finalization of the codebook to reflect this step, and single coding of primary themes of the discussion, coding for subthemes, exploring any emerging themes, calculating the frequency of subthemes by using the matrix method, and drawing out quotes from the coded phrases [59]. The survey team will then produce a summary report of the findings.

Study Monitoring and Quality Assurance

Study monitoring will be conducted by staff of FHI 360 and the research firms. At FHI 360, the study will be led by the study manager who is responsible for overall study administration, ensuring the availability of study resources (funding and staff) and for providing feedback and final decisions related to execution of the study. PIs will oversee technical aspects of the study, conduct overall monitoring of data collection, and ensure quality as well as review and sign off on key deliverables and coordinate activities at the regional level to ensure consistency across study sites. The PI or co-PI will also be responsible for identifying, documenting, and reporting protocol violations and social harm. Country research staff of Alive & Thrive will manage all aspects of the study in the assigned country and serve as the linkage between FHI 360 and the research firms.

In the national research firm, the study manager is responsible for technical and financial oversight as well as overall study management in accordance with the signed contract. During data collection, field supervisors will be responsible for ensuring that proper informed consent is provided to each participant and that data collection processes are followed in compliance with the protocol. Field supervisors will remain with the data collection team at all times. Field supervisors will carefully check that the consent process is being performed as approved. The PI will check with field supervisors every week. Field supervisors will travel with selected data collection teams to monitor their field work and to answer any questions during data collection, providing feedback to these teams, as needed.

The research study will be conducted in full compliance with the protocol, which will not be amended without prior approval by the PI or co-PI. Protocol violations will be documented on protocol violation reporting forms, and all will be reported to and addressed by the research teams as soon as possible following discovery. They are also responsible to ensure continuous safety monitoring of all research study participants and for alerting the protocol team if unexpected concerns arise. Compliance will also be checked during site visits by the PI or co-PI.

Ethical Considerations

From study design to the dissemination of findings, we will follow the ethical guidelines of the Helsinki Declaration [60]. The protocol, questionnaires, IDI guides, consent form, other requested documents, and any subsequent modifications will be reviewed and approved by the institutional review boards (IRBs) of FHI 360 and in-country Ethical Committees. The investigators will make safety and progress reports to the local IRB at least annually and within 3 months after termination or completion. After completing the interview, we will give the interviewees a gift or amount of money (US $2-$3) to thank them and recognize their participation in this research.

Results

This study was funded in June 2018 and approved by the relevant IRBs (FHI 360: April 16, 2019 and May 18, 2020; and Hanoi University of Public Health: December 6, 2019). Data collection will occur on the following date(s): Vietnam: November and December 2019, May and June 2020; the Philippines: projected August 2020; Myanmar and Thailand: pending based on permissions and funding. Expected results are to be published in January 2021. As of July 2020, we had enrolled 1150 participants in Vietnam.

We will analyze the data using a study conceptual model (Figure 2). We will present a comparison of key contents of the policies across countries and against international standards and recommendations as well as a comparison of implementation strategies, coverage, monitoring, and enforcement across countries. We will also present data analyzed using an interrupted time-series approach to quantify the change in the slope or level of selected outcomes before and after the effective date of a new or amended policy. Findings from IDI contents will include themes, subthemes, and quotes from the coded phrases. For the surveys with women, we will present associations between exposure to maternity protections (eg, taking leave, duration of leave, paid leave, lactation support at work, social norms) and infant and young child feeding practices. We will also present associations between exposure to infant formula promotion (eg, advertisement, advice, gifts) and infant and young child feeding practices as well as women's intentions, knowledge, beliefs, social norms, and self-efficacy.

Key results from the study will then be contextualized within the conceptual model (Figure 2) for further examination of the structural and environmental determinants of breastfeeding behavior, namely how regulation (or not) of marketing and promotion of BMS might affect social and cultural perceptions and social norms around breastfeeding and how maternity protection and working environments support or impede breastfeeding.

The results will be disseminated through meetings with relevant ministries, institutions, and local and international NGOs in the study countries as well as within FHI 360. Study results are intended to be used by ministries and local stakeholders to advocate for relevant policy changes to improve maternity protection and strengthen the Code in the study countries and the Southeast Asia region. Findings will also be disseminated as presentations in scientific forums and in peer-reviewed publications to contribute to the global discourse of nutrition policy making.

Discussion

Strengths and Limitations

The unique strengths of this study are that it examines multiple countries, uses mixed methods, and considers 2 main policies relating to maternal, infant, and young child nutrition: the Code and maternity protection. We will collect and analyze various components from perinatal care, breastfeeding practices, behavioral determinants (eg, intentions, trials, adoption, and maintenance), and exposure to various types of interventions. We adapted standardized questionnaires, including those from the WHO NetCode Assessment Module and ILO Maternity Protection Assessment Toolkit to facilitate the comparison with other studies. We structured the research protocol and data collection tools into sections, which will allow their adaptation to other contexts and study purposes. In addition to tools relating to the data collection (Multimedia Appendices 1-6), we also included a PowerPoint presentation to summarize the study (Multimedia Appendix 7).

Yet, the study has limitations, which we recognize. Because the selection of provinces and districts will not be random, our results may only apply to study sites. Further, the cross-sectional design of the survey cannot be used to conclude causal relationships. However, we have increased the plausibility of causality by selecting age ranges for which exposure or covariate variables occurred before or at about the same time as the studied practices. In addition, if available, secondary data of repeated surveys or trend data analysis will be used to strengthen the causality by ensuring temporal criteria (eg, have data before and after the policy enactment).

Conclusion

This study will increase understanding of the effectiveness of policy interventions to address the structural determinants of breastfeeding, namely national policies on maternity protection and the Code. By assessing the potential impact of these policies and bottlenecks for successful implementation through the perspective of various stakeholders, including policymakers, implementors, and beneficiaries, this study will build an evidence base that can be used to advocate for stronger policy adoption and enforcement in study countries and beyond.

Acknowledgments

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Authors' Contributions

TN, AW, and RM designed the study. TN, AW, JC, HT, and RM wrote the initial protocol. All authors provided critical intellectual feedback to help revise the manuscript. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Semi-quantitative policy data extraction form.
[PDF File (Adobe PDF File), 216 KB - resprot_v9i9e21286_app1.pdf]

Multimedia Appendix 2
In-depth interview guides.
[PDF File (Adobe PDF File), 450 KB - resprot_v9i9e21286_app2.pdf]

Multimedia Appendix 3
Images to facilitate in-depth interviews.
[PDF File (Adobe PDF File), 2020 KB - resprot_v9i9e21286_app3.pdf]

Multimedia Appendix 4
Survey questionnaire for pregnant women.
[PDF File (Adobe PDF File), 468 KB - resprot_v9i9e21286_app4.pdf]

Multimedia Appendix 5
Survey questionnaire for women with children aged 0-11 months.
[PDF File (Adobe PDF File), 559 KB - resprot_v9i9e21286_app5.pdf]

Multimedia Appendix 6
Informed consents.
[PDF File (Adobe PDF File), 364 KB - resprot_v9i9e21286_app6.pdf]

Multimedia Appendix 7
PowerPoint presentation of the study.
[PDF File (Adobe PDF File), 783 KB - resprot_v9i9e21286_app7.pdf]

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Abbreviations

BMS: breast milk substitute
DHS: Demographic Health Surveys
IDI: in-depth interview
ILO: International Labor Organization
IRB: Institutional Review Board
MICS: Multiple Indicator Cluster Surveys
NGO: non-governmental organization
PI: principal investigator
PIN: personal identification number
PSU: primary sampling unit
UN: United Nations
UNICEF: United Nations Children's Fund
WHA: World Health Assembly
WHO: World Health Organization

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Protocol

Online Navigation for Pre-Exposure Prophylaxis via PleasePrEPMe Chat for HIV Prevention: Protocol for a Development and Use Study

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Abstract

Background: Pre-exposure prophylaxis is an HIV medication taken by an individual who is HIV-negative to prevent infection before exposure to the virus. Numerous clinical studies in various communities have shown high rates of effectiveness when pre-exposure prophylaxis is taken as prescribed. Since FDA (US Food and Drug Administration) approval of the first product for pre-exposure prophylaxis in 2012, uptake has been lower than the estimated 1.1 million US adults who could benefit from its use, with an estimated 70,394 individuals on pre-exposure prophylaxis in 2017. Of these, only 11% were Black and 13% were Hispanic despite Black and Hispanic individuals comprising two-thirds of individuals who could benefit, highlighting racial and ethnic disparities in pre-exposure prophylaxis uptake. Patient navigators have been shown to be effective in improving the linkage and retention in care outcomes of people living with HIV across the HIV treatment cascade and can be used throughout the pre-exposure prophylaxis care continuum to assist decision making and connect potential users to pre-exposure prophylaxis services.

Objective: PleasePrEPMe Chat was designed as a novel online strategy aimed at improving engagement in pre-exposure prophylaxis care services with pre-exposure prophylaxis–eligible populations in California via free HIV-prevention information and health care navigation services.

Methods: Visitors connected with navigators via online bilingual (English, Spanish) chat. During the chat, navigators helped locate pre-exposure prophylaxis services through the PleasePrEPMe provider directory, provided links to HIV-prevention resources, and supported uninsured, insured, and undocumented visitors with benefits navigation. Data such as date, time, type of encounter, visitor type, key demographics, discussion topics, insurance, and other relevant information were collected via a chat log and through the HealthEngage chat platform.

Results: From April 2017 to December 2019, PleasePrEPMe completed 2191 online chats. Mean interaction time was 16 minutes, with 68% of chats covering more than one topic. Conversation topics included health care navigation (1104/2191, 50.39%), provider identification (954/2191, 43.54%), pre-exposure prophylaxis information (773/2191, 35.28%), post-exposure prophylaxis information (318/2191, 14.91%), and the California Pre-Exposure Prophylaxis Assistance Program (232/2191, 10.59%). Referrals to pre-exposure prophylaxis– or non pre-exposure prophylaxis–related resources included directory updates, HIV testing and treatment, undetectable=untransmittable, reproductive health, sexually transmitted infections, and other prevention methods. A total of 368 chat visitors completed a voluntary satisfaction scale rating the quality and helpfulness of the service provided, producing a mean rating of 4.7 out of 5.

Conclusions: Online chat is a method for reaching people not already engaged in HIV-prevention services, supporting HIV-prevention decision making, and linking people seeking information online with in-person services. Additional research to evaluate online sexual health information services and understand how social determinants of health influence online engagement is needed to better understand how to reach priority populations not well served by current HIV-prevention services.

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KEYWORDS

pre-exposure prophylaxis: PrEP; online chat; health systems navigation; HIV prevention; online navigation

Introduction

Background

Pre-exposure prophylaxis is a regimen of HIV medications taken by an HIV-negative individual to prevent infection before an exposure to the virus. Numerous clinical studies in various communities have shown high rates of effectiveness when pre-exposure prophylaxis is taken as prescribed, as outlined in the US Public Health Service's guidelines [1].

Since FDA (US Food and Drug Administration) approval of the first product for HIV pre-exposure prophylaxis in 2012, uptake has been lower than the Centers for Disease Control and Prevention's (CDC) estimated 1.1 million US adults who could benefit from its use [2], with an estimated 70,394 individuals on pre-exposure prophylaxis in the fourth quarter of 2017 [3]. Black and Hispanic individuals comprise two-thirds of individuals that the CDC estimates could benefit from pre-exposure prophylaxis, yet 68% of pre-exposure prophylaxis users are white, while 11% are Black and 13% are Hispanic [2]. California lags behind the national average for decreases in new HIV diagnoses: from 2011-2016, the number of new HIV diagnoses fell 5.7% nationally, while the number in California dropped less than half of that—2.6% [4-6].

The pre-exposure prophylaxis care continuum is a framework by which to assess pre-exposure prophylaxis uptake and includes 3 phases: awareness (identify individuals at highest HIV risk, enhance self-perceived HIV risk awareness, raise pre-exposure prophylaxis awareness), uptake (facilitate pre-exposure prophylaxis access, link to pre-exposure prophylaxis care, prescribe pre-exposure prophylaxis, initiate pre-exposure prophylaxis), and adherence and retention (adhere to pre-exposure prophylaxis, retention in pre-exposure prophylaxis care) [7]. Although various pre-exposure prophylaxis care continua have been described and published [7-9], gaps exist due to the lack of scientific consensus on the best measures for pre-exposure prophylaxis program implementation.

Patient navigators have been shown to be effective in improving the linkage and retention in care outcomes of people living with HIV [10]. Similarly, patient navigators may provide support throughout the pre-exposure prophylaxis care continuum by assisting decision making and connecting potential pre-exposure prophylaxis users to pre-exposure prophylaxis services [11]. Navigation is generally defined as providing support for insurance, health care, and medication access and can range from a passive referral to active case management. HIV-prevention education and health benefits navigation may help ensure that potential pre-exposure prophylaxis users access adequate insurance coverage, state and local government pre-exposure prophylaxis services, and industry-sponsored co-pay and other medication assistance programs.

Internet usage is ubiquitous—across ages, races, and geographical regions [12]. Smartphone-based geospatial networking apps are a common method for finding sex partners among gay and bisexual men [13]. Rates of condomless anal sex and multiple sex partners are higher among people who connect with partners online [14], which highlights the potential impact of employing novel online strategies to improve engagement in pre-exposure prophylaxis care services with pre-exposure prophylaxis–eligible populations. Web-based interventions are increasingly being studied as methods for reaching individuals about sensitive topics and stigmatized issues such as HIV. For example, a web-based self-help intervention supplemented by brief chat counseling was shown to be an effective alternative to in-person counseling in supporting people with cannabis-use problems [15]. A systematic review [16] showed that electronic health interventions that address the prevention of HIV and other sexually transmitted infections (STIs) among men who have sex with men are impactful on changing short-term behavior.

PleasePrEPMe Chat

The PleasePrEPMe website provides HIV-prevention information, training resources, and referrals, including a searchable, location-responsive pre-exposure prophylaxis provider directory [17] and tailored resource pages for potential pre-exposure prophylaxis users, frontline pre-exposure prophylaxis navigation staff, and medical providers. With this library of resources, PleasePrEPMe sought to expand web-based services to support people who seek HIV-prevention information and to link them to appropriate resources. PleasePrEPMe also features live chat services (PleasePrEPMe Chat) to reach potential pre-exposure prophylaxis users online in California and to facilitate their access to pre-exposure prophylaxis.

This paper describes the process of developing PleasePrEPMe Chat, an online chat service that helped potential users of pre-exposure prophylaxis understand their options and connect with pre-exposure prophylaxis–related care, as well as the quality assurance process and initial findings as of December 31, 2019. Specifically, this paper describes the multistep chat flow process by which PleasePrEPMe Chat engaged visitors online and the post-chat follow-up.

Methods

Funding

PleasePrEPMe Chat was launched in April 2017, in collaboration with Project Inform and the Office of AIDS, California Department of Public Health, as a way for people to access bilingual confidential and free HIV-prevention information and health care navigation services online, removing the need to visit a clinic or provider for immediate health education and benefits navigation support. The California

Department of Public Health provided funding to PleasePrEPMe. PleasePrEPMe subcontracted with Project Inform—a national community-based organization with 30 years of experience providing essential HIV treatment and prevention information (including a community helpline)—to develop this online model for providing health information and pre-exposure prophylaxis navigation services.

Privacy Protection

PleasePrEPMe utilized various technologies and procedures to ensure the privacy of an individual's personal health information, as defined in the Health Insurance Portability and Accountability Act (HIPAA) of 1996. (HIPAA establishes national standards to protect individuals' personal health information and requires safeguards to protect the privacy of personal health information.) In support of these protections, PleasePrEPMe utilized the HIPAA-compliant, online chat management platform HealthEngage to administer the various aspects of on- and off-hours chat operations. The HealthEngage platform provided a user-friendly dashboard for PleasePrEPMe navigators to manage chats as it also records chat transcripts and collects internet-related data.

Procedure

PleasePrEPMe Chat was staffed by one full-time bilingual (Spanish and English) navigator. Backup navigators were on call when chat visitors required one-on-one attention, chat volume was high, chat interactions transitioned to telephone calls, extensive research and follow-up was required, or the primary navigator was managing chats in multiple languages. Communications that support visitor navigation services among PleasePrEPMe staff, which include personal health information, took place through HIPAA-secure email or Zoom, a web-based video conferencing platform that complies with HIPAA standards. Real-time communications without personal health information took place in the messaging platform Slack.

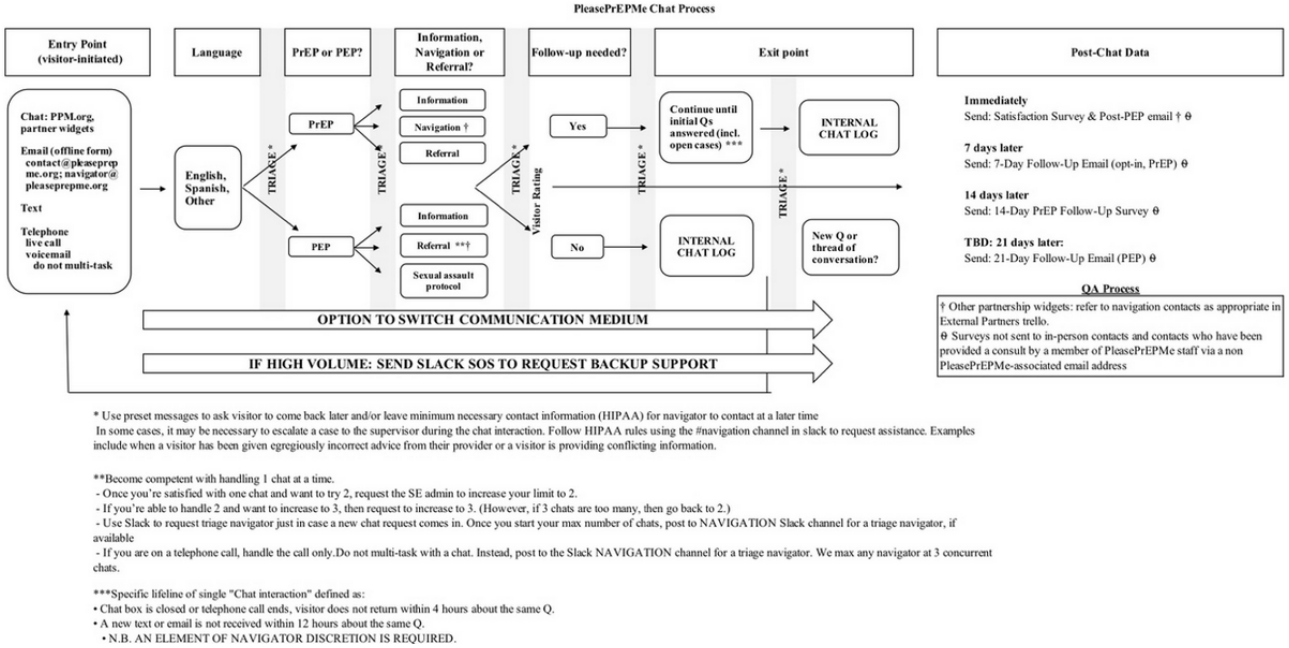
Via online bilingual chat, navigators helped locate pre-exposure prophylaxis services through the PleasePrEPMe provider directory, provided links to HIV-prevention resources including educational material, and supported uninsured, insured, and undocumented visitors with benefits navigation. Open hours of operation for live chat were Monday-Friday, 9 AM to 5 PM (Pacific Time). Chats could be anonymous, although additional chats, email, text, and telephone follow-up were offered to visitors to augment the initial chat conversation or complete the navigation process.

During open hours, visitors with a California Internet Protocol (IP) address from their internet-access devices (computers, cell phones, other handhelds) who land on any webpage of the PleasePrEPMe website were offered *proactive chat*, whereby the chat box opened after 1 second on the web page offering to initiate chat. Automated messaging informed visitors that by engaging in chat they agreed to the website's documented terms of use. Providing an email address was not required to chat, and chats could be completely anonymous. However, some passive data collection of IP addresses was undertaken by the HealthEngage platform. Visitors with IP addresses outside California and all visitors during offline hours could manually click on the chat button to complete a brief data collection form that generated an email message to PleasePrEPMe staff. The offline form included the user agreement for the terms of use. While PleasePrEPMe promoted chat as the primary method of online communication, staff could also be contacted for navigation services via the PleasePrEPMe website contact form, staff email, text, telephone, or social media.

Chat Flow

The chat flow chart represents a multistep process (Figure 1) by which visitors could engage with PleasePrEPMe online: service entry point, language screening, triaging post-exposure prophylaxis indication, core pre-exposure prophylaxis services, follow-up agreement, chat exit point, and post-chat follow-up.

Figure 1. PleasePrEPMe Chat Process. PEP: post-exposure prophylaxis; PrEP: pre-exposure prophylaxis; Q: question; QA: quality assurance.



Entry Point

The primary entry point for a visitor into a PleasePrEPMe Chat encounter was through proactive chat or offline messages. Visitor emails received through the website's contact form page, navigator email links, text message, telephone call, or voicemail could have been an entry point for a new encounter.

Language Screening

Preferred language (English, Spanish) was assessed with each visitor through the HealthEngage platform, and Google Translate was utilized for other languages when needed.

Post-exposure Prophylaxis Triage

PleasePrEPMe Chat encounters were initially triaged to determine if there was a recent HIV exposure within the previous 72 hours that warranted a conversation about post-exposure prophylaxis information and navigation rather than pre-exposure prophylaxis. (Post-exposure prophylaxis is a combination HIV regimen that is taken after a potential exposure to HIV, not before as with pre-exposure prophylaxis.)

Core Services

Both pre-exposure prophylaxis and post-exposure prophylaxis encounters included services from 3 program categories: information provision (eg, HIV 101, pre-exposure prophylaxis 101, and other such basic information), navigation assistance (eg, health system information, insurance benefits, financial assistance programs), and referrals provision (eg, finding clinicians and colocated programs such as gender-affirming services). PleasePrEPMe chats often included support from more than one category. Additionally, a sexual assault protocol supported PleasePrEPMe staff with navigating applicable cases.

Follow-up Agreement

Prior to closing the chat, the navigator assessed if the visitor desired follow-up information, such as receiving clinician contact information, detailed explanations of complicated insurance questions, referrals to assistance programs, or web links to additional content on discussed topics. Contact information—usually email—was collected for follow-up. The navigator would verify the information to be provided at follow-up.

Chat Exit Point

At the conclusion of an encounter, the HealthEngage platform offered visitors a textbox with the option of providing feedback with a rating out of 5 stars. Once the chat was closed, PleasePrEPMe staff completed a PleasePrEPMe chat log (Textbox 1) using data collected through HealthEngage and chat content, such as date, time, type of encounter, visitor type, key demographic data, discussion topics, insurance, and other relevant information. Once the chat log was completed, if the visitor returned with an inquiry, it was treated as a new encounter, beginning at the entry point. Visitors could switch the PleasePrEPMe chat medium (ie, from chat to phone) and PleasePrEPMe staff could also offer this to a visitor, particularly in a post-exposure prophylaxis situation.

Textbox 1. PleasePrEPMe chat log.

- Time stamp, date
- PleasePrEPMe staff member responding to initial request
- Medium initial request initiated via (chat, offline message, email message, telephone call, text, or other)
- Medium encounter continued via (chat, email, telephone call, text, or other), visitor contact information (email address or telephone number)
- Zip code
- City
- State
- Language (English, Spanish, other)
- Visitor type (pre-exposure prophylaxis or post-exposure prophylaxis user or potential user, non-clinical staff person, clinician)
- PleasePrEPMe chat topics covered (pre-exposure prophylaxis or post-exposure prophylaxis navigation, identified a specific medical provider/clinic, provider database entry or update, referral to non-navigation resources, treatment as prevention or undetectable equals untransmittable, reproductive health, HIV treatment 101, HIV testing/HIV 101, condoms and/or other prevention methods, other STIs, California's Pre-Exposure Prophylaxis Assistance program, other)
- Initial question
- Insurance type (commercial, employer/private), Medi-Cal/Medicaid, Medicare, Veterans Administration, uninsured, not known, other
- Coding for level of PleasePrEPMe Chat (question was answered by PleasePrEPMe directory, question about sexual health or pre-exposure prophylaxis navigation, question required additional investigation and follow-up, question required post-exposure prophylaxis navigation or other emergency assistance, and non-navigation administrative question)

Post-chat Follow-up

Once the PleasePrEPMe chat log was completed and if follow-up was needed, staff composed and delivered (eg, via email) the follow-up content as requested during the chat immediately for those seeking post-exposure prophylaxis and within 12 hours of the encounter for those seeking pre-exposure prophylaxis.

Depending upon the follow-up provided, one or two post-chat questionnaires (ie, Satisfaction Survey, 14-Day Pre-Exposure

Prophylaxis Follow-up Survey) were sent using Google forms, and data automatically populated into a secure form on Google Drive. All questionnaires were available in both Spanish and English.

The first questionnaire (Satisfaction Survey; see Multimedia Appendix 1) was emailed to all visitors who provided an email address. The Satisfaction Survey assessed visitor experience with PleasePrEPMe chat service and referrals, identified how the visitor heard about PleasePrEPMe, and collected optional demographic information and feedback for improving services, including whether PleasePrEPMe helped them make decisions around their prevention needs. Visitors were given the option to provide their demographic information.

A second questionnaire, the 14-Day Pre-Exposure Prophylaxis Follow-up Survey (see Multimedia Appendix 2), was emailed to those who were provided referrals to clinicians. The 14-Day Pre-Exposure Prophylaxis Follow-up Survey was designed to assess the next steps in their access to pre-exposure prophylaxis care and prescription, including barriers they encountered, while providing another opportunity for PleasePrEPMe to continue supporting the visitor's needs and receive feedback. PleasePrEPMe sent a 14-Day Pre-Exposure Prophylaxis Follow-up Survey to individuals who (1) provided an email address, (2) did not opt out of receiving future surveys, and (3) originally received a referral to a pre-exposure prophylaxis provider.

In January 2020, PleasePrEPMe emailed a retrospective questionnaire (see Multimedia Appendix 3) to the 1017 chat visitors who both chatted and provided email contact information between April 24, 2017 and December 31, 2019. The survey was designed to assess the utility of PleasePrEPMe's services, gather feedback for service improvement, and understand other barriers to pre-exposure prophylaxis and post-exposure prophylaxis access. The survey was tailored to the experiences of potential pre-exposure prophylaxis users and frontline workers who assist individuals seeking pre-exposure prophylaxis with branching questions for each group (as self-identified) to answer. Individuals who did not remember their encounter with PleasePrEPMe were not eligible to respond. All eligible participants were offered the opportunity to opt into a drawing for a US $100 Visa gift card.

Quality Assurance

Quality assurance protocols ensured the provision of accurate information and high levels of customer service throughout encounters with visitors. PleasePrEPMe employed several methods of quality assurance. First, at the close of a chat encounter, HealthEngage offered visitors a 5-star rating system with a textbox to provide optional feedback on their encounter. For any negative feedback received, staff reached out to those with an email address to provide additional support. Second, internal quality assurance reviews were performed on every encounter for new navigators and on a randomly selected number of encounters for experienced navigators. Internal quality assurance identified gaps in encounter consultations, resources or support for visitors, and areas for improvement and growth. Third, monthly internal quality assurance reviews were completed on a selected number of chats. The primary navigator assigned 3 to 5 transcripts and any follow-up emails to each team member for review. Team members utilized an Internal Quality Assurance Review Survey to review encounters (see Multimedia Appendix 4), such as providing suggestions for improvement (briefer responses, missed opportunities, use of transitional wording, more clarity, etc). Results of the monthly quality assurance review were discussed in team meetings, including recommendations for updates to protocols or content. Furthermore, PleasePrEPMe's Director of Content and Quality provided quarterly reviews of the internal quality assurance forms, any negative feedback from surveys, and any challenging PleasePrEPMe chats flagged by staff. A report and discussion from this quarterly review was discussed in scheduled staff meetings. The chat process and post-chat follow-up questionnaires were approved by the University of California, San Francisco Human Research Protection Program Institutional Review Board.

Results

From April 24, 2017 to December 31, 2019, PleasePrEPMe received 2991 chats; 755 were unrelated or incomplete chats, where incomplete information was received to allow for service provision, including truncated chats where PleasePrEPMe could not share information; consumer requests for information outside our areas of expertise; offline messages without enough data to reply; and system tests, and 45 chats were duplicate chats (for example, visitor left an offline message but also completed an online chat soon afterwards). We analyzed the 2191 complete chats. Chat user information is shown in Table 1.

Table 1. PleasePrEPMe Chat user information.

Category and type	Total, n (%)
All users	2991 (100)
Unrelated or incomplete[a]	755 (25.24)
Duplicate[a]	45 (1.50)
Complete	2191 (73.25)
Service type (n=2191)	
Online live chat	1465 (66.86)
Offline chat form	309 (14.10)
Email	283 (12.92)
Telephone call or text	70 (3.19)
Other (social media, in person, etc)	64 (2.92)
User location (n=2191)	
California	1674 (76.40)
Other states	422 (19.26)
Outside the United States	59 (2.69)
Unable to collect location data	36 (1.64)
Language (n=2191)	
English	1960 (89.46)
Spanish	224 (10.22)
English and Spanish	5 (0.23)
Dutch (via Google Translate)	1 (0.05)
Chinese (via Google Translate)	1 (0.05)
Visitor type (n=2191)	
Pre-exposure prophylaxis/post-exposure prophylaxis consumer or potential consumer	1585 (72.34)
Nonclinical staff person or frontline pre-exposure prophylaxis navigation worker	510 (23.28)
Clinical provider	80 (3.65)
Unknown	16 (0.73)
Insurance (n=2191)	
Commercial insurance	447 (20.40)
Uninsured	302 (13.78)
Medicare/Medicaid	172 (7.85)
Other (Veterans Administration/TRICARE or student health insurance)	10 (0.46)
Multiple	9 (0.41)
Unknown	1251 (57.10)

[a]Not included in subsequent calculations.

Online chats lasted a mean of 16 minutes (ranging from 8 seconds to 93 minutes), and topics varied across most chats while often covering more than one topic within chats (68%). PleasePrEPMe utilized an internal list of topic areas to categorize conversations. Topline topics included health care navigation (1104/2191, 50.39%), provider identification (954/2191, 43.54%), pre-exposure prophylaxis information (773/2191, 35.28%), post-exposure prophylaxis information (318/2191, 14.51%), and the California Pre-Exposure Prophylaxis Assistance Program (232/2191, 10.59%). Referrals to pre-exposure prophylaxis– or non pre-exposure prophylaxis–related resources included directory updates, HIV testing and treatment, undetectable=untransmittable, reproductive health, sexually transmitted infections, and other prevention methods. Chat content data are shown in Table 2.

Table 2. PleasePrEPMe Chat topic information.

Topic and description	Total[a], n (%)
All chats	2191 (100)
Health care navigation and coverage options	1104 (50.39)
Identifying specific providers in the directory	954 (43.54)
Pre-exposure prophylaxis information, safety, effectiveness, side effects, dosing, adherence	773 (35.28)
Post-exposure prophylaxis information, safety, effectiveness, side effects, dosing, adherence	318 (14.51)
California Pre-Exposure Prophylaxis Assistance Program	232 (10.59)
Referrals to pre-exposure prophylaxis– or non pre-exposure prophylaxis–related resources	
Directory updates	175 (7.99)
HIV testing or treatment/HIV 101	165 (7.53)
Undetectable=untransmittable	62 (2.83)
Reproductive health	44 (2.01)
Other STIs	34 (1.55)
Other prevention	26 (1.19)
Not recorded	25 (1.14)

[a]Because a chat may include multiple topics, percentage will not equal 100.

Quality Assurance and Improvement Measures

At the conclusion of a chat, within the chat platform visitors were offered an opportunity to rate the quality of the service on a scale ranging from 1 (not helpful at all) to 5 (very helpful) and to provide a comment. Of those offered the scale, 368 chat visitors participated, producing a mean rating of 4.7 out of 5.

Of 871 people who were sent the Satisfaction Survey, 85 (9.8%) responded. Of these, 75 (88.2%) responded “agree” or “strongly agree” to the statement, “PleasePrEPMe met my needs.” On the item, “How likely are you to refer a friend/colleague to PleasePrEPMe.org?” 75 (88.2%) responded “very likely” or “likely.” On the item, “PleasePrEPMe helped me make decisions about my HIV prevention, or helped me to help others around their HIV-prevention needs,” 67 people (78.8%) responded “agree” or “strongly agree.”

Of 515 people who were sent the 14-Day Pre-Exposure Prophylaxis Follow-up Survey, 25 (4.9%) responded. Of these, 19 (76%) had contacted a clinician since connecting with PleasePrEPMe, 10 (40%) had obtained a pre-exposure prophylaxis prescription, 7 (28%) were currently on pre-exposure prophylaxis, and all 7 were very satisfied with their decision to start. Reasons for not starting pre-exposure prophylaxis varied, with the reasons stated most frequently (4 of 14 given) being insurance and cost issues, provider delays such as long waitlists, not hearing back from clinics, or unsupportive providers.

Of the 1017 individuals who were sent a retrospective questionnaire, 74 completed questionnaires were received; 63/74 (85.1%) recalled their encounter—37 (59%) chatted on behalf of themselves, 25 (40%) on behalf of a client or for some other reason, and 1 (1.6%) did not remember. From the group of 37, 17 started pre-exposure prophylaxis or post-exposure prophylaxis after chatting, and PleasePrEPMe was able to help 14 of these respondents with getting or staying on pre-exposure prophylaxis or post-exposure prophylaxis. From the group of 25, PleasePrEPMe was able to help the client in 16 cases, 23 respondents were satisfied or very satisfied with PleasePrEPMe's knowledge level, and 21 were satisfied or very satisfied with PleasePrEPMe’s referral to resources.

Discussion

Pre-exposure prophylaxis is a highly effective option to prevent HIV infection for those who are vulnerable to the virus and are aware of this relatively new development in biomedical prevention [1]. Employing patient navigators within medical and nonmedical services improves linkage to and retention in HIV care for people living with HIV [10]. Web-based interventions that aim to improve health outcomes around sensitive and stigmatizing issues such as sexual health and HIV are also increasingly being utilized [16,17]. PleasePrEPMe implemented a bilingual online program for people to access confidential, sex-positive, free HIV-prevention information and health care navigation services, with the goal to decrease the rate of new HIV infections [6,7]. PleasePrEPMe developed a chat program by incorporating several key approaches: offering a vetted search engine of pre-exposure prophylaxis providers, creating and providing data-driven content, utilizing available online technologies, adapting HIPAA-compliant standards to ensure privacy, and employing quality assurance methods to maintain and improve service provision.

Between April 2017 and December 2019, the PleasePrEPMe online chat navigation program (augmented by email, phone, and text) supported nearly 2200 individuals with sexual health questions. Potential consumers, frontline staff, and medical providers initiated a chat from various devices (laptop, cell phone, handheld) through a pop-up form on PleasePrEPMe’s and partners’ websites. PleasePrEPMe’s bilingual navigator

tailored responses to questions and issues posed, and maintained chats until visitors had their needs addressed.

Online chat topics varied, with the topics most frequently discussed being health care navigation, medical provider identification, pre-exposure prophylaxis and post-exposure prophylaxis information, and patient financial support resources such as the California Pre-Exposure Prophylaxis Assistance Program. Topics also included HIV testing and treatment, undetectable=untransmittable, reproductive health, sexually transmitted infections, and other prevention methods.

Nearly half of the visitors received referrals. Satisfaction with the information and referrals provided by PleasePrEPMe was high. The majority of users believed they were helped with making decisions and that PleasePrEPMe met their needs. PleasePrEPMe was rated as highly helpful.

The nature of pre-exposure prophylaxis access challenges seen in California may be different and not generalizable to states without Medicaid expansion or where the overall culture may be more politically conservative. The issues and solutions around health care navigation that PleasePrEPMe encountered while assisting chat visitors from California may differ from those in other states. Additional research is needed to evaluate how novel services such as PleasePrEPMe are utilized by people who seek sexual health information and services online. Research can also help understand how social determinants of health [18] may or may not influence a person to engage in these services, and how to maximally leverage online marketing and outreach to reach priority populations currently underserved by traditional programs.

Online chat reaches people who were not already engaged in or need support with accessing HIV-prevention services. Chat also supported visitor education and decision making, linking individuals with appropriate in-person services. PleasePrEPMe aimed to reach people seeking to address their sexual health needs online, to support them with decision making, and to link them with in-person and online providers as needed. This approach could ease the need to visit a clinic or provider for health education and benefits navigation that can be handled online. It also helps to resolve challenges that some people encounter around pre-exposure prophylaxis access, including insurance and payment issues, confidentiality, and stigma.

HIV-prevention conversations must necessarily include pre-exposure prophylaxis and post-exposure prophylaxis navigation to holistically serve the needs of visitors at all stages in the pre-exposure prophylaxis care continuum.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
PleasePrEPMe satisfaction survey.
[DOCX File , 42 KB - resprot_v9i9e20187_app1.docx]

Multimedia Appendix 2
PleasePrEPMe 14-day PrEP follow-up survey.
[DOCX File , 26 KB - resprot_v9i9e20187_app2.docx]

Multimedia Appendix 3
PleasePrEPMe retrospective survey.
[DOCX File , 70 KB - resprot_v9i9e20187_app3.docx]

Multimedia Appendix 4
PleasePrEPMe internal quality assurance review survey.
[DOCX File , 27 KB - resprot_v9i9e20187_app4.docx]

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Abbreviations

AIDS: acquired immunodeficiency syndrome
CDC: Centers for Disease Control and Prevention
HIPAA: Health Insurance Portability and Accountability Act
HIV: human immunodeficiency virus
IP: internet protocol
STI: sexually transmitted infection

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Protocol

Mobile Fitness and Weight Management Apps: Protocol for a Quality Evaluation

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Abstract

Background: Obesity is a contributing factor for many noncommunicable diseases and a growing problem worldwide. Many mobile apps have been developed to help users improve their fitness and weight management behaviors. However, the speed at which apps are created and updated means that it is important to periodically assess their quality.

Objective: The purpose of this study is to evaluate the quality of fitness and weight management mobile health apps using the Mobile Application Rating Scale (MARS). It will also describe the features of the included apps and compare the results to a previous evaluation conducted in 2015.

Methods: Searches for “fitness,” “weight,” “exercise,” “physical activity,” “diet,” “eat*,” and “food” will be conducted in the Apple App Store and Google Play. Apps that have been updated over the past 5 years will be included. Two reviewers will rate the apps’ quality using the MARS objective and subjective quality subscales. Interrater reliability will also be assessed. Features included in high-quality apps will be assessed, and changes in quality, features, and behavior change techniques made during the past 5 years will be described.

Results: The results will be included in the evaluation paper, which we aim to publish in 2020.

Conclusions: This evaluation will assess the quality of currently available fitness and weight management apps.

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KEYWORDS

mobile apps; telemedicine; smartphone; exercise; weight loss; obesity; physical fitness; fitness trackers

Introduction

The number of people who are overweight or obese has tripled since 1975, and in 2016, 40% of adults were overweight [1]. Obesity is a major concern for public health because it increases the likelihood of many preventable diseases (eg, cardiovascular diseases, diabetes, osteoarthritis, and some cancers) and places an economic burden on the health care system [1,2]. However, obesity is largely a preventable condition [3]. Increasing physical activity and eating healthier foods can help people to manage their weight, and thus reduce the consequences of chronic and preventable diseases [1,4].

Since the first smartphone was released in 2008, digital technologies have become an increasingly common and popular way for people to change their health behaviors [5]. Mobile apps are a useful platform to provide behavioral interventions to improve fitness and weight because of the widespread use of smartphones and the large number of mobile health apps

available [6]. Some evidence of the acceptability and effectiveness of mobile health apps for increasing physical activity, improving eating behaviors, and reducing weight has been found [4,7], but additional evidence is still needed to strengthen the conclusion that mobile apps are effective at improving health outcomes in particular [8-10]. The mixed body of evidence of effectiveness might be due to the fact that higher engagement has been found to be related to increased adherence to the app and weight loss [4]. Therefore, it is important to assess the quality of mobile fitness and weight management apps because quality is likely to influence engagement, which will affect the effectiveness of these apps at changing behavior and causing weight loss.

Evaluations have previously examined the quality of mobile weight management apps [11,12]. However, testing for these evaluations was conducted in August 2014 [12] and the beginning of 2015 [11]. Given the rate at which apps are being developed and updated [13], evaluations should be conducted every couple of years to assess the quality of currently popular mobile fitness and weight management apps. Evaluations can then be compared to track whether there have been any changes in the quality or features of popular apps over time. Both of the previous evaluations assessed popular iOS and Android apps. Bardus et al [11] evaluated the apps using the MARS subscales and found that the overall quality of apps was moderate, while Chen et al [12] focused on Australian apps and concluded that the overall quality was suboptimal. The authors of both reviews also examined the behavior change techniques (BCTs) [14] that were incorporated in the apps. Experts have established a theory-based taxonomy of these BCTs to aid identification and evaluation of the key components of behavioral interventions [14]. The review of Australian apps found a general lack of BCTs [12], while self-monitoring of behavior and outcomes, goal setting for behavior and outcomes, and feedback on behavior and outcomes were identified as the most common BCTs in Bardus et al's review [11].

In their evaluation, Bardus et al [11] concluded that improvements could be made to app quality by focusing on information quality and evidence-based content. A similar, more current evaluation will provide an update on both the quality of mobile fitness and weight management apps and which BCTs are included in them. This will allow an assessment of whether and how mobile fitness and weight management apps have changed in the past 5 years. There are also improvements that can be made to the previous review methodologies: Bardus et al's evaluation [11] only included apps that focused on a combination of diet and physical activity interventions and had a version available in both the Apple App Store and Google Play, while Chen et al's review [12] did not use a standardized overall measure of app quality (the MARS measure was not yet published [15]). The proposed evaluation will broaden that scope by also including apps that focus on only diet or physical activity and apps available only in the App Store or Google Play, as this will better represent the broad range of apps that people use to improve their fitness and weight management. Additionally, our evaluation will compare our findings with Bardus et al's [11] to examine how the general state of app quality and the inclusion of BCTs have changed in the past 5 years.

Therefore, this evaluation will be focused on three main research questions. First, what is the objective and subjective quality of various Apple and Android mobile fitness and weight management apps, as measured by the Mobile Application Rating Scale? Second, what are the features most commonly associated with high-quality apps? Third, how have the quality and included BCTs of popular apps changed since 2015?

Methods

Overview

We will use the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) guidelines [16] to guide the search and selection of apps for evaluation. This evaluation will be composed of an app search, app selection, data extraction, data analysis, and data synthesis.

Search Strategy

We will search the Apple App Store and Google Play to identify current popular mobile fitness and weight management apps. We will search each of the following keywords: "fitness," "weight," "exercise," "physical activity," "diet," "eat*," and "food." These were chosen based on commonly used terms in the literature [4]. The search results will be filtered by popularity (based on the stores' display algorithms) and the 100 most popular apps from each search will be screened. This will ensure that the apps being evaluated are the ones that are most used and will limit the number of apps to be evaluated.

Eligibility

Inclusion Criteria

We will include popular apps that aim to improve health-related fitness and weight management behaviors, specifically diet or physical activity, and that target the general population. This will include apps designed for any age group, from children to older adults.

Exclusion Criteria

We will exclude duplicates (if an app is available for both iOS and Android operating systems, we will include the iOS version only) and apps that are not in English. We will also exclude apps that have not been updated in the past 5 years [17]. We will exclude any apps that do not provide dietary or physical activity behavioral interventions that aim to improve general health and fitness or weight management. Therefore, recipe apps, athletic training apps, and apps that are focused on behaviors that are not health-related (like looking younger) will be excluded. Apps that are focused on specific populations (eg, people with specific diseases or pregnant women) will also be excluded.

Screening and App Selection

All of the apps found in the search will be recorded in an Excel document (Microsoft Corp) and duplicates will be removed, including Android apps that also have an iOS version. Preliminary screening by two independent reviewers will

determine initial eligibility for the evaluation using the information provided in the app summaries on the App Store and Google Play. Apps that are deemed eligible will be downloaded. Apps that, upon closer examination, do not meet the inclusion criteria will also be excluded. Any disagreements between the reviewers will be discussed and, if necessary, settled by a third reviewer. All of the apps identified as being eligible for inclusion will be reviewed. A PRISMA flow diagram will be used to record the details of the search, screening, and selection processes so that the evaluation can be reproduced.

Data Extraction

The apps will be tested and evaluated by two independent reviewers. Each app will be used for at least half an hour before being rated using the MARS scales [15,18]. The reviewers will also extract general information about the app as well as its features (eg, how it tracks behaviors or outcomes; if it provides notifications, feedback, or information) and any BCTs [14] that are included. The items to be extracted are summarized in Textbox 1.

Textbox 1. Data that will be extracted from the apps.

General information

- Year of development
- Platform (iOS, Android, etc)
- Developers
- Target population
- Target behavior change (eg, diet, step count, exercise)
- Cost
- Number of downloads
- App Store or Play Store rating

Features

- App features (eg, notifications, tracking, feedback)
- Behavior change techniques (BCT Taxonomy v1 [14])

Quality (all are Mobile Application Rating Scale subscales [15])

- Engagement
- Functionality
- Visual esthetics
- Information quality
- Subjective quality

Data Analysis and Synthesis

The Mobile Application Rating Scale will be used to evaluate the quality of the included apps. Both reviewers will complete a training exercise in the MARS (which will be requested from the corresponding author of the MARS development paper) before conducting the evaluation [15]. The MARS has a total of 23 items split into 5 different subscales: engagement, functionality, esthetics, information, and subjective quality. Each item is rated on a 5-point Likert scale. The overall score is calculated by averaging the mean scores of the subscales, with objective and subjective ratings kept separate [15]. Interrater reliability of the two reviewers will also be assessed.

The objective and subjective scores of the various apps will be compared to determine which apps have the highest quality. The features and BCTs of the 20 highest-rated apps will also be examined, to determine which features are associated with the highest-quality apps.

Results

The results will be included in the evaluation paper, which we aim to publish in 2020.

Discussion

A systematic evaluation of mobile fitness and weight management apps will provide a clearer assessment of their quality. There are many fitness and weight management apps to choose from, and star rating systems have not been found to be strongly correlated with the MARS measure of app quality [15]. An evaluation of these apps will help consumers choose higher quality apps and will contribute to the literature on and the improvement of mobile health behavior change apps by examining which features and BCTs [14] are common in high-quality apps. These results will be compared to a previous evaluation of the quality of and BCTs included in mobile weight management apps and describe whether and how popular apps have changed since 2015 [11]. Based on the data, this section

will compare the included apps, discuss the limitations of the evaluation, and consider important directions for future research. One limitation that can already be identified is the use of only two reviewers. Given the significant time requirements to evaluate each app in depth, it is only feasible to use two reviewers; although the reviewers will work independently, it is possible that they will be biased in a way that might not be identified.

Acknowledgments

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Authors' Contributions

EM, CL, and MMI conceived the study topic and designed the review protocol. MMI prepared the first draft of the protocol with revisions from MHVV and EM.

Conflicts of Interest

None declared.

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Abbreviations

BCT: behavior change technique
MARS: Mobile Application Rating Scale
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols

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Protocol

Effects of an Overground Walking Program With a Robotic Exoskeleton on Long-Term Manual Wheelchair Users With a Chronic Spinal Cord Injury: Protocol for a Self-Controlled Interventional Study

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Abstract

Background: In wheelchair users with a chronic spinal cord injury (WU_{SCI}), prolonged nonactive sitting time and reduced physical activity—typically linked to this mode of mobility—contribute to the development or exacerbation of cardiorespiratory, musculoskeletal, and endocrine-metabolic health complications that are often linked to increased risks of chronic pain or psychological morbidity. Limited evidence suggests that engaging in a walking program with a wearable robotic exoskeleton may be a promising physical activity intervention to counter these detrimental health effects.

Objective: This study's overall goals are as follows: (1) to determine the effects of a 16-week wearable robotic exoskeleton–assisted walking program on organic systems, functional capacities, and multifaceted psychosocial factors and (2) to determine self-reported satisfaction and perspectives with regard to the intervention and the device.

Methods: A total of 20 WU_{SCI}, who have had their injuries for more than 18 months, will complete an overground wearable robotic exoskeleton–assisted walking program (34 sessions; 60 min/session) supervised by a physiotherapist over a 16-week period (one to three sessions/week). Data will be collected 1 month prior to the program, at the beginning, and at the end as well as 2 months after completing the program. Assessments will characterize sociodemographic characteristics; anthropometric parameters; sensorimotor impairments; pain; lower extremity range of motion and spasticity; wheelchair abilities; cardiorespiratory fitness; upper extremity strength; bone architecture and mineral density at the femur, tibia, and radius; total and regional body composition; health-related quality of life; and psychological health. Interviews and an online questionnaire will be conducted to measure users' satisfaction levels and perspectives at the end of the program. Differences across measurement times will be verified using appropriate parametric or nonparametric analyses of variance for repeated measures.

Results: This study is currently underway with active recruitment in Montréal, Québec, Canada. Results are expected in the spring of 2021.

Conclusions: The results from this study will be essential to guide the development, implementation, and evaluation of future evidence-based wearable robotic exoskeleton–assisted walking programs offered in the community, and to initiate a reflection regarding the use of wearable robotic exoskeletons during initial rehabilitation following a spinal cord injury.

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International Registered Report Identifier (IRRID): DERR1-10.2196/19251

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KEYWORDS

assistive technology; locomotion; spinal cord injury; rehabilitation; robotics; osteoporosis

Introduction

Deleterious Effects of Nonactive Sitting Time and Reduced Physical Activity

Approximately 100,000 Canadians are currently living with a *spinal cord injury* (SCI) and nearly 4000 new cases are reported annually in Canada [1]. Individuals affected by an SCI usually experience sensory, motor, and autonomic impairments that challenge their walking and walking-related abilities. Despite intensive initial rehabilitation, regaining effective walking ability is challenging for most [2,3]. Indeed, many individuals will not regain their ability to walk due to trunk and lower extremity paralysis or severe paresis. For others, the cardiorespiratory, muscular, or balance requirements needed to walk are too great to achieve a sufficient distance (~183-677 m) or velocity (~0.44-1.32 m/s) for ambulation within their home or in the community [4]. Hence, they will generally use a powered or manually propelled wheelchair as their main mode of mobility. The prolonged, nonactive sitting time [5] and the reduction or cessation of physical activity [6,7] typically linked to this mode of mobility contribute to the development or exacerbation over time of complex and chronic secondary health problems. These health problems often effect the cardiorespiratory [8-12], musculoskeletal [13-17], and endocrine-metabolic [18-23] systems. Moreover, they are often coupled with raised risks of nociceptive or neuropathic pain [24,25] or psychological morbidity [26] (eg, increased depressive symptoms). In turn, these negatively affect functional skills and capacity as well as psychosocial factors in long-term *wheelchair users with a chronic SCI* (WU_{SCI}) [27], while also increasing the risk of premature mortality and the burden on caregivers. It is no surprise that these impacts come with substantial financial costs, estimated to be between CAD $1.5 million and $3 million (~US $1.1-$2.3 million) per person with an SCI in the Canadian health care system [28].

Inventory of Rehabilitation and Physical Activity Interventions

Given the increased life expectancy owing to improvements in medical treatment, along with the growing population of individuals with SCI, there have been recent calls to direct additional attention to the cascade of cardiorespiratory, musculoskeletal, and endocrine-metabolic health problems faced by this population and to interventions targeting modifiable factors linked to these problems [29-31]. To date, most rehabilitation and physical activity interventional studies aiming to mitigate these health problems can be grouped within three main categories: (1) static standing activities using frames with or without full-body vibrations [32], (2) dynamic standing activities combining braces, body-weight support, functional electrical stimulation, or robotic exoskeleton systems for treadmill ambulation with various degrees of lower extremity weight bearing [33-36], and (3) lower extremity or trunk neuromuscular electrical stimulation for cycling or rowing in a sitting position [37,38]. Scoping and systematic reviews confirm that most of these interventions were tested among relatively small and heterogeneous samples of individuals with SCI over relatively short periods of time (ie, ≤12 weeks) [30]. They also highlight that superiority, equivalence, and noninferiority trial designs have rarely been used and no clear consensus has yet emerged on the best possible interventions for a given individual at a specific time within the continuum of care [30]. Nonetheless, based on the currently available evidence, it is relatively well established among WU_{SCI} that the following is true:

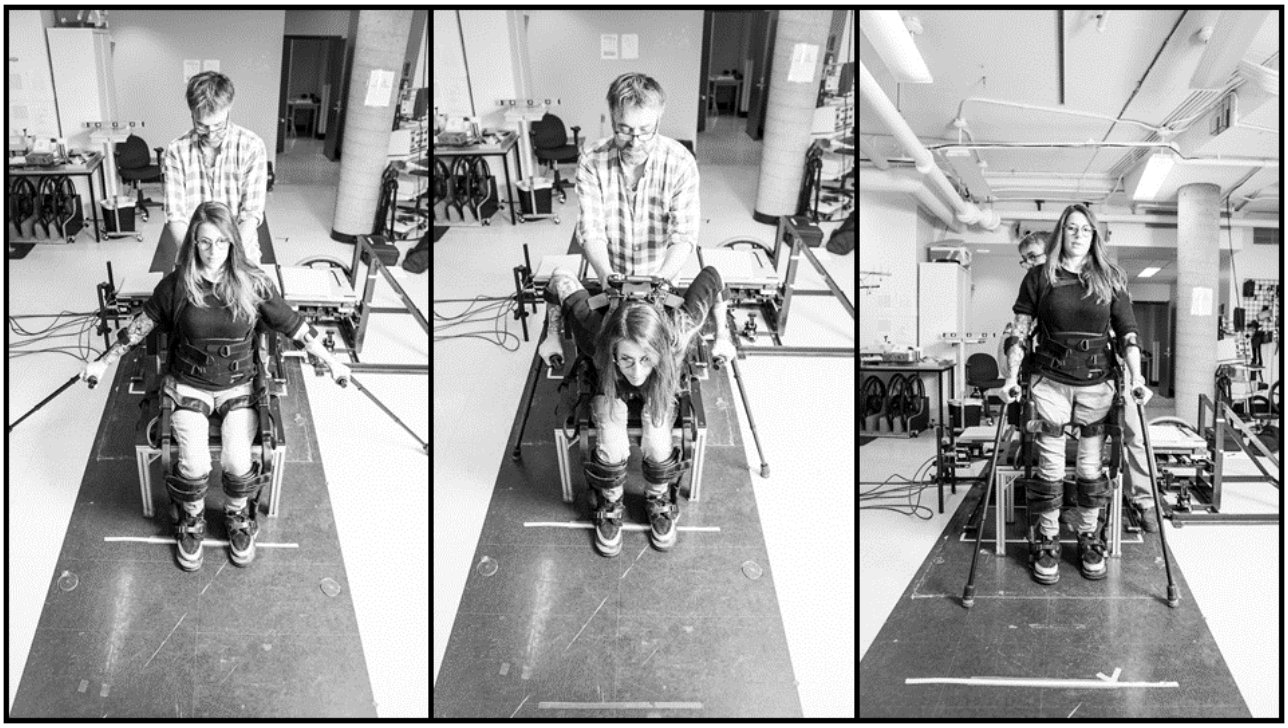
1. Gravity-derived high-standing loads, as well as impacts resulting even from low walking speeds [39], are the prominent sources of adaptive stimuli for bone health and surpass the effects linked to static standing or resistance training alone (eg, functional electrical stimulation) [40].
2. Two to three sessions per week of regular structured exercise at moderate-to-vigorous intensity for at least 20 minutes, plus upper body strength exercise (ie, three sets of 10 repetitions at 50%-80% of the one-repetition maximum for large muscle groups), improve cardiorespiratory and endocrine-metabolic health [41-43]. Increasing this exercise intensity is expected to potentiate these beneficial effects [44].

Wearable Robotic Exoskeletons as a Promising Intervention

Commercially available wearable robotic exoskeletons, an assistive technology allowing WU_{SCI} to stand and walk overground (see Figure 1), now offer opportunities for clinicians and scientists to develop novel activity-based physical activity programs articulated around overground walking and walking-related abilities [45,46]. Though only small-scale studies are currently available, including a feasibility study from our lab, with most focusing on walking performance [45-54], emerging evidence suggests that performing sit-stand transfers,

standing, and walking with a wearable robotic exoskeleton promote lower extremity mechanical loading and mobility. The gravity exposure and muscle elongation-relaxation cycles at the lower extremities signal the mechanosensitive osteocytes and regulate the bone remodeling process via bone formation and reabsorption (ie, mechanotransduction process) [55]. Additionally, the performance of these functional abilities with a wearable robotic exoskeleton solicits the large trunk, thoracohumeral, and upper extremity muscles [56] (ie, *strengthening exercise*) via three mechanisms: (1) maintenance of standing balance, which is even more difficult as the center of mass is moved upward and backward given the configurations of the wearable robotic exoskeleton, (2) control of anterolateral body-weight shifts required to safely initiate the steps, and (3) unloading lower extremities to smooth heel contact with the ground at heel strike. Walking with a wearable robotic exoskeleton also increases the energy expenditure need (ie, *aerobic exercise*) [57-59]. By coupling these types of exercises, walking with a wearable robotic exoskeleton may lead to beneficial cardiorespiratory, musculoskeletal, and endocrine-metabolic [60,61] adaptations in WU_{SCI}. In addition, a growing body of evidence suggests that cognitive and executive [62] as well as psychological [63,64] benefits can be anticipated, as favorable associations with physical activity, especially aerobic exercise, have been documented. Also of interest, WU_{SCI} have expressed high levels of satisfaction with wearable robotic exoskeleton–assisted walking programs and have positively perceived the wearable robotic exoskeleton learnability and usability [64]. To what extent these health benefits may have positive synergistic effects on their functional capacities and psychosocial well-being is unclear. How to best configure wearable robotic exoskeleton–assisted walking programs (eg, number, frequency, duration, and intensity of sessions) while conciliating them with the perspectives of WU_{SCI} to potentiate the outcomes of such programs also remains elusive.

Figure 1. Wearable robotic exoskeleton for sit-stand transitions and overground walking manufactured by Ekso Bionics.



Objectives

The *overall goals* of this study, using mixed methods, are as follows: (1) to determine the immediate and short-term effects of a 16-week overground wearable robotic exoskeleton–assisted walking program on organic systems, functional capacities, and multifaceted psychosocial factors among WU_{SCI} living in the community, and (2) to determine self-reported satisfaction and perspectives with regard to the intervention and the device. The *specific objectives* are articulated around four research questions and hypotheses:

1. Question 1: Does a 16-week walking program with the wearable robotic exoskeleton induce beneficial changes on musculoskeletal, cardiorespiratory, and endocrine-metabolic health; wheelchair-related functional skills and mobility; and psychosocial outcomes? Hypothesis 1: It is hypothesized that beneficial effects observed during the postintervention and retention measurement times will significantly and meaningfully exceed any changes observed during the control and preintervention measurement times (ie, T_0 [control measurement time] vs T_1 [preintervention measurement time] vs T_2 [postintervention measurement time] vs T_3 [retention measurement time]).
2. Question 2: What personal factors best determine and predict the beneficial effects of the walking program with the wearable robotic exoskeleton? Hypothesis 2: It is hypothesized that the individuals with the highest level of SCI and the longest time since the SCI (ie, possibly the best determinants and predictors) will be those who respond best to the walking program.

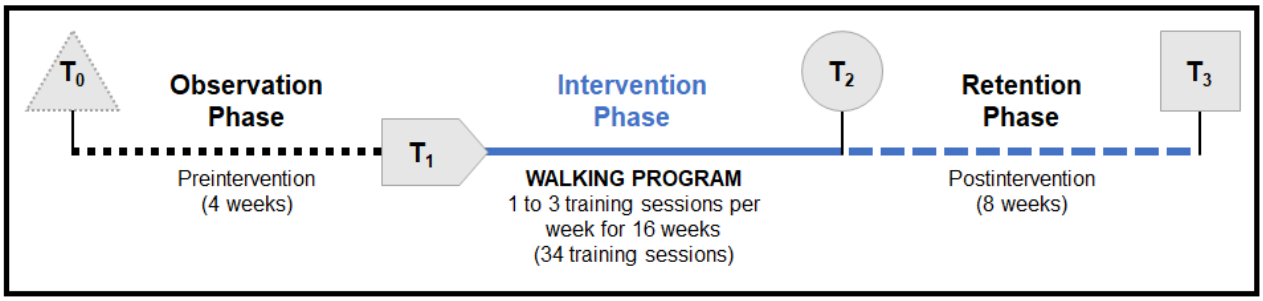
3. Question 3: What program attributes best determine and predict the beneficial effects of the walking program with the wearable robotic exoskeleton? Hypothesis 3: It is hypothesized that the total number of steps taken will be the best determinant and predictor of the measured changes.
4. Question 4: What are the participants' satisfaction levels with the walking program and the wearable robotic exoskeleton itself, and what are the expectations regarding its future use in the context of a home- or community-based adapted physical activity program? Hypothesis 4: It is hypothesized that WU_{SCI} will (1) express high levels of satisfaction with the walking program using the wearable robotic exoskeleton and with the wearable robotic exoskeleton itself and (2) report on how they envision its future in the context of home- or community-based use to shape the development of an adapted physical activity program in the future.

Methods

Study Design

A prospective, longitudinal, self-controlled interventional study with multiple discrete measurement times will be used to assess outcomes at baseline (ie, preintervention phase), during the intervention, and thereafter (ie, retention phases) (see Figure 2). While this design may contrast with *classic* study designs frequently recommending a separate comparison group to assess efficacy or effectiveness, the use of a separate comparison group was judged as nonideal in the context of this study, based on the challenges linked to the classification and quantification of the severity of SCIs and their heterogeneous consequences [65]. In addition, interventional trials of new technologies document that potential participants are reluctant to participate, refuse to adhere to the requirements of a control group, or withdraw for the most part from a control group [66,67]. To strike an optimal balance between the need to have a control group with the anticipated strong desire of potential participants to engage in the wearable robotic exoskeleton–assisted walking program, while also considering the amount of, and timeline limits linked to, the study's funding, the study includes a 4-week observation phase prior to the start of the intervention. Since only individuals with a chronic SCI with *stable* overall health status and life habits will be recruited, outcome measures will be assessed at the start and at the end of the 4-week observation phase. These outcome measures will provide data about each participant's natural variability and will enable us to detect whether the intervention has an effect greater than the underlying natural variability (ie, patient-specific minimal detectable change criteria computed); they will also enable us to test the effects of the intervention (ie, pre- vs postintervention responses). This boosts the ethical acceptability of the project, minimizes the impacts of potential and unmeasured confounding variables, facilitates recruitment, and mitigates the risk of experimental attrition. Lastly, semistructured interviews and an online questionnaire will capture participants' satisfaction levels and perspectives about the wearable robotic exoskeleton–assisted walking program and the mobility technology in itself (ie, the wearable robotic exoskeleton).

Figure 2. Summary of the design of the study along with the different assessment times. T_0: control measurement time; T_1: preintervention measurement time; T_2: postintervention measurement time; T_3: retention measurement time.



Participants and Inclusion and Exclusion Criteria

We aim to recruit a nonprobabilistic consecutive sample of 20 long-term WU_{SCI}. The inclusion and exclusion criteria are listed in Textbox 1. Initial screening is conducted by phone to establish eligibility based on criteria developed during the feasibility study. Once deemed eligible from the initial clinical screening, potential participants attend a short assessment to confirm eligibility.

Textbox 1. Inclusion and exclusion criteria.

Participant-specific inclusion criteria:

- Adults (≥18 years old)
- Chronic complete or incomplete traumatic or nontraumatic spinal cord injury (SCI) at least 18 months before enrollment
- Long-term manual wheelchair use as primary means for in-house and community mobility (ie, nonambulatory)
- Understand and communicate in English or French
- Reside or will arrange for temporary housing in the community within 75 km from the main research site

Participant-specific exclusion criteria:

- Other neurological impairments aside from those linked to the SCI (eg, multiple sclerosis)
- Concomitant or secondary musculoskeletal impairments (eg, hip heterotopic ossification)
- History of lower extremity fracture within the past year
- Unstable cardiovascular or autonomic system
- Renal insufficiency
- Pregnancy
- Any other conditions that may preclude lower extremity weight-bearing, walking, or exercise tolerance in the wearable robotic exoskeleton

Exoskeleton-specific inclusion criteria:

- Body mass: ≤100 kg
- Height: 1.52-1.93 m
- Pelvis width: 30-46 cm
- Thigh length: 51.0-61.4 cm
- Lower leg length: 48.0-63.4 cm

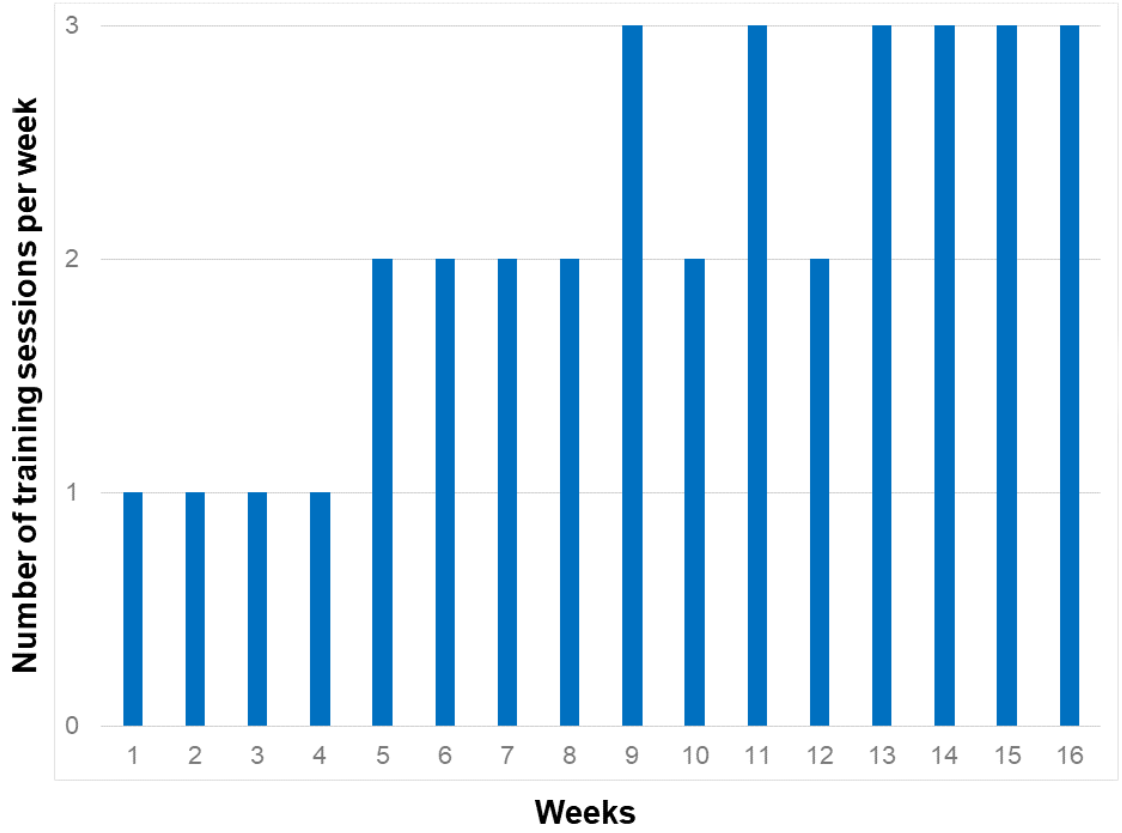
Exoskeleton-specific exclusion criteria:

- Inability to sit with hips and knees at ≥90° flexion
- Lower extremity passive range of motion limitations (hip flexion contracture ≥5°, knee flexion contracture ≥10°, and ankle dorsiflexion ≤–5° with knee fully extended)
- Moderate-to-severe lower extremity spasticity (score of >3 on the Modified Ashworth Scale)
- Length discrepancy (≥1.3 cm or ≥1.9 cm at the thigh or lower leg segment, respectively)
- Skin integrity issues preventing wear of the wearable robotic exoskeleton

Intervention: Overground Wearable Robotic Exoskeleton–Assisted Walking Program

An Ekso GT (Ekso Bionics) wearable robotic exoskeleton, which has been approved by Health Canada, is used in this study (see Figure 1). At T_1, participants engage in a wearable robotic exoskeleton–assisted overground walking program that encompasses 34 training sessions offered over a 16-week period. The number of training sessions per week progressively increases to safely and efficiently adhere to the overload principle (see Figure 3). The duration of the training program mimics that of a recent study that confirms for the first time an improvement in bone turnover among individuals with a chronic SCI following a 16-week walking program [39]. The frequency of the training program that progresses from one to three sessions per week matches the latest recommendation from the Physical Activity Guidelines for Adults with SCI, including the new conditional recommendation to engage in at least 30 minutes of moderate-to-vigorous intensity aerobic exercise three times per week for cardiometabolic health benefits [68]. All training sessions are supervised by a certified physiotherapist as well as a physiotherapy assistant as needed [46,53]. During each 60-minute training session, participants perform sit-stand transfers and walk with the wearable robotic exoskeleton and a walking aid (ie, rolling walker or forearm crutches). Verbal and tactile feedback are provided by the physiotherapist as needed.

Figure 3. Progression of the number of training sessions per week during the 16-week walking program.



Total hip areal bone mineral density (aBMD), determined with dual-energy x-ray absorptiometry (DXA) scans performed at T_1, is used to assign each participant to one of three training regimes based on lower extremity fracture risks [69]: (1) conservative (T-score ≤ –2.5; first session includes a maximum of 300 steps; number of steps progresses up to 10% every week), (2) moderate (–2.5 < T-score < –1.0; first session includes a maximum of 400 steps; number of steps progresses up to 15% every week), or (3) aggressive (T-score ≥ –1.0; first session includes a maximum of 500 steps; number of steps progresses up to 20% every week). Workload is further individualized depending on each participant's level of proficiency and tolerance; it is progressively and safely increased by modifying walking parameters (eg, number of steps, speed, and duration) or reducing total resting time or level of assistance provided by the physiotherapist to maintain a moderate-to-vigorous training intensity (ie, rate of perceived exertion ≥3/10 on the Modified Borg Scale [70]). Training parameters are recorded at the end of each session (eg, total standing time, total walking time, total number of steps, assistance provided, and rate of perceived exertion). Given the risks of adverse events inherently linked to the use of a wearable robotic exoskeleton [69,71], skin integrity at interface pressure points, particularly at the tibial tuberosity, and signs of inflammation at the ankle and knee joints before and after each training session, respectively, are assessed and any serious adverse events will be reported.

To be considered as having successfully completed the program, at least 75% of the training sessions (ie, 26/34) need to have been completed. To this effect, to assure an optimal attendance rate similar to the one reached during the feasibility study (ie, attendance rate was 97.7%) [72] and to overcome one of the most commonly reported barriers to intervention studies (ie, transportation), participants have three key options: (1) driving their own car or being transported by car by a family member or a friend with free parking provided within 50 meters from the entrance, (2) using public transit, or (3) scheduling trips with the adapted transport free services.

Outcomes: Domains, Tools, Measures, and Assessment Times

Overview

All outcomes reflecting the potential impacts of the intervention based on the logic model (see Figure 4) are prospectively collected at T_0, T_1, T_2, and T_3, except the participants' satisfaction levels and perspectives and the endpoint interviews, which are only completed at T_2. Outcomes are collected by a registered physiotherapist (AB) who has been trained with standardized data collection protocols adapted for WU_{SCI}. All selected outcomes are commonly used in clinical trials targeting similar domains and populations—most have been used in the feasibility study—and most are summarized, including psychometric properties, and are recommended by well-established medical, rehabilitation, or psychosocial research organizations and networks [73]. A summary of all outcomes included in this study and the times at which they are administered is provided in Table 1. The following subsections describe all outcomes in detail.

Figure 4. Project-specific logic model highlighting the relationships between the different domains of interest and related outcome measures. L/E: lower extremity; SCI: spinal cord injury; U/E: upper extremity; WRE: wearable robotic exoskeleton.

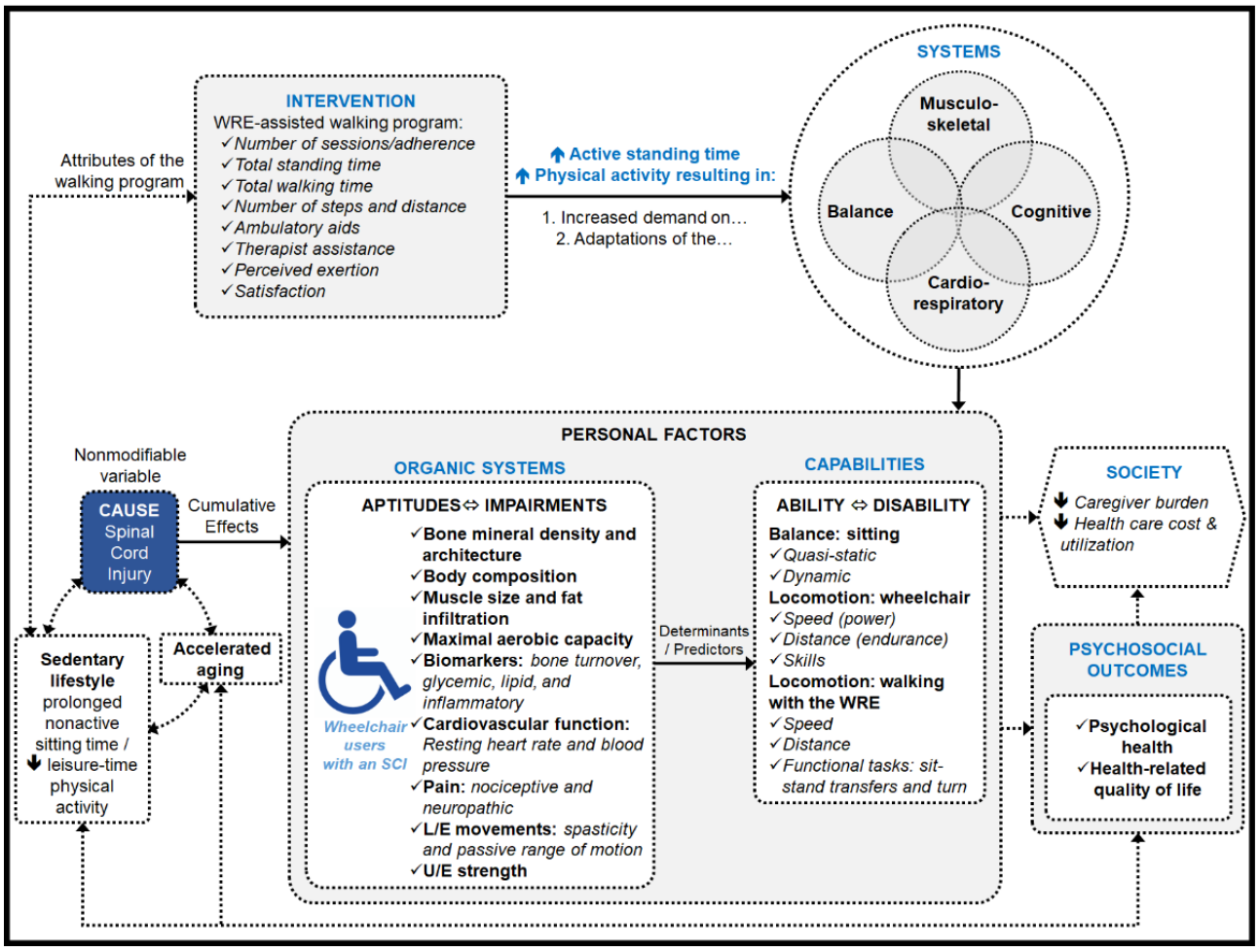


Table 1. Summary of outcomes.

Outcomes	Measurement times[a]			
	T_0	T_1	T_2	T_3
Clinical assessments				
Personal characteristics				
Sociodemographic characteristics (age, sex, etc)	✓			
Neurological impairment (American Spinal Injury Association Impairment Scale)	✓			
Anthropometric parameters (weight and height)	✓			
Resting heart rate and blood pressure	✓	✓	✓	✓
Pain (International SCI [spinal cord injury] Pain Basic Dataset version 2.0)	✓	✓	✓	✓
Passive range of motion at the ankle, knee, and hip joints (two-axis goniometer)	✓	✓	✓	✓
Spasticity (Modified Ashworth Scale)	✓	✓	✓	✓
Wheelchair abilities				
20-meter wheelchair propulsion test (natural and maximal speeds)	✓	✓	✓	✓
Slalom test	✓	✓	✓	✓
6-minute manual wheelchair propulsion test	✓	✓	✓	✓
Laboratory assessments				
Bone mineral density and architecture				
Dual-energy x-ray absorptiometry (hip and lumbar vertebrae)	✓	✓	✓	✓
Peripheral quantitative computed tomography (proximal tibia, distal femur, and proximal radius)	✓	✓	✓	✓
Body composition				
Dual-energy x-ray absorptiometry (total body)	✓	✓	✓	✓
Muscle quality				
Peripheral quantitative computed tomography (intramuscular fat infiltration)	✓	✓	✓	✓
Blood biomarkers				
Bone turnover (serum procollagen type 1 N-terminal peptide, osteocalcin, C-terminal cross-linking telopeptide, and 25-hydroxyvitamin D)	✓	✓	✓	✓
Glycemia (fasting glucose, insulin, and glycosylated hemoglobin)	✓	✓	✓	✓
Insulin resistance (homeostatic model assessment)	✓	✓	✓	✓
Lipids (total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, and apolipoprotein B)	✓	✓	✓	✓
Inflammation (C-reactive protein, tumor necrosis factor alpha, interleuken-6, and interleuken-10)	✓	✓	✓	✓
Cardiorespiratory fitness				
Respiratory gas analysis during 6-minute manual wheelchair propulsion test		✓	✓	
Total distance travelled during the 6-minute manual wheelchair propulsion test	✓	✓	✓	✓
Take-home assessments				
Psychological health				
World Health Organization Quality of Life assessment	✓	✓	✓	✓
Beck Depression Inventory	✓	✓	✓	✓
Beck Anxiety Inventory	✓	✓	✓	✓
Psychological General Well-Being Index	✓	✓	✓	✓
Participant satisfaction and perspectives				
Updated version of the Montreal Walking Exoskeleton Satisfaction and Perspectives Questionnaire			✓	
Semistructured interview			✓	

[a]Measurement times: T_0 (control measurement time), T_1 (preintervention measurement time), T_2 (postintervention measurement time), and T_3 (retention measurement time).

Clinical Assessments

Personal Characteristics

Assessments are completed at the different assessment times to collect outcomes characterizing the following:

1. Sociodemographic characteristics (eg, age; sex; time since injury; history of fragility fracture; medications, including opioid analgesia, benzodiazepines, or unfractionated heparin; current smoking status; and alcohol intake) [74].
2. Neurological impairment (eg, American Spinal Injury Association Impairment Scale for neurological level, motor and sensory scores, and severity) [75].
3. Anthropometric parameters (eg, weight and height).
4. Resting heart rate and systolic and diastolic blood pressure using an electronic sphygmomanometer machine [76].
5. Pain using the *International SCI Pain Basic Dataset version 2.0*, which includes a set of core questions for up to three separate pain problems experienced over the past week and three questions on perceived pain interference with activities, mood, and sleep [77].
6. Passive range of motion at the ankle, knee, and hip joints with a two-axis goniometer (ie, contracture).
7. Upper extremity muscle strength (ie, pushing and pulling strength with a wheelchair wheel attached to an instrumented dynamometer and handgrip strength with a handheld dynamometer).
8. Lower extremity spasticity using the *Modified Ashworth Scale* [78].

Wheelchair Abilities

Wheelchair abilities are assessed using the following performance-based wheelchair propulsion tests: (1) 20-meter wheelchair propulsion test (natural and maximal speeds), (2) slalom test, and (3) 6-minute manual wheelchair propulsion test [79-82]. The slalom test is used as a surrogate of trunk control since forward reaching distance is a good determinant (r=–0.75) [80] and trunk control is known to be the best predictor of multidirectional seated limits of stability during reaching (R^2=0.95) [83]. The *Wheelchair Skills Test Questionnaire version 5.0* [84] is used as well to assess wheelchair abilities. This questionnaire assesses 34 wheelchair mobility and wheelchair-related skills. Each skill is rated on a 4-point self-reported scale: responses to the question *Can you do it?* include 0 (no), 1 (partially), 2 (yes), and 3 (very well). A capacity score is calculated (0%-100%), reflecting the number of skills that can be partially or completely done. Moreover, it assesses how confident—*How confident are you?* 0 (not at all), 1 (partly), 2 (moderately), or 3 (very)—and how often—*How often do you do it?* 0 (never), 1 (occasionally), 2 (usually), or 3 (always)—each skill is performed to calculate confidence and performance scores (0%-100%).

Laboratory Assessments

Bone Mineral Density and Architecture

A DXA system (Lunar Prodigy, GE Healthcare) is used to calculate aBMD at the hip, femoral neck, and the first to the fourth lumbar vertebrae [85]. Moreover, T-scores compare the measured aBMD values of each participant against values predicted from a matched reference group for sex, age, and ethnicity and are expressed as the number of SDs (ie, z scores or T-scores depending on age of participant). Measurements of aBMD and z scores or T-scores are directly provided by the system's software.

In addition, a peripheral quantitative computed tomography (pQCT) system (XCT 3000, Stratec Biomedical Systems) is used to characterize the volumetric bone mineral density (vBMD) and the microarchitecture parameters of trabecular and cortical bones at various imaging sites: 66% of the tibia, 25% of the femur, and 66% of the radius. These sites were chosen to maximize muscle circumference in each scan [86]. To minimize site-selection error between measurement times, images are taken using a standardized protocol including scout views with recommended reference lines [86]. As per current recommendations, reported pQCT outcomes will minimally include the following: total trabecular and cortical mineral content; cortical cross-sectional area and thickness; and biomechanical strength indices calculated from density and area (ie, bone strength indices, polar section modulus, and polar strength strain index) [86]. Outcomes are calculated using a validated open source image analysis software package (Fiji distribution of ImageJ) [87,88].

Body Composition

Whole-body scans obtained with the DXA system are used to quantify total and regional (ie, upper extremities, trunk, and lower extremities) body fat and fat-free (ie, lean) tissue mass and relative percentages, respectively [89]. These measures are directly provided by the DXA system's software.

Muscle Quality

Cross-sectional images of the femur, tibia, and radius captured with the pQCT system are also used to measure the muscle size (ie, cross-sectional area) and intramuscular fat infiltration (ie, muscle density) using the same validated open source image analysis software [87,88].

Blood Biomarkers

Fasting blood samples (ie, >8-hour fast) are used to quantify bone turnover biomarkers (ie, serum procollagen type 1 N-terminal peptide, osteocalcin, C-terminal cross-linking telopeptide, and 25-hydroxyvitamin D), glycemic biomarkers (ie, fasting glucose, insulin, and glycosylated hemoglobin), insulin resistance biomarkers (ie, homeostatic model assessment), lipid biomarkers (ie, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, and apolipoprotein B), and inflammatory biomarkers (ie, C-reactive protein, tumor necrosis factor alpha, interleuken-6, and interleuken-10).

Cardiorespiratory Fitness

At T_1 and T_2, participants complete the 6-minute manual wheelchair propulsion test wearing a gas analyzer system (COSMED K4b2, COSMED srl). This portable system incorporates a sealed face mask placed over the mouth and nose and anchored around the head, a telemetric stationary O_2 and CO_2 gas analyzing unit, and a battery harnessed to the anterior and posterior thorax. This system is calibrated before each test as recommended by the manufacturer. For the other two measurement times (ie, T_0 and T_3), the total distance travelled during the 6-minute manual wheelchair propulsion test is used as a surrogate measure of cardiorespiratory fitness since it has been found to strongly correlate and agree with the maximal arm-crank test (r=0.92; mean difference 0.21 ±1.94 mL/kg·min) [90].

Take-Home Assessments

Psychological Health

For the psychosocial outcomes, health-related quality of life is measured with the short version of the *World Health Organization Quality of Life* assessment [91-94]. This includes 24 questions organized around four domains: physical health (seven items), psychological health (six items), social relationships (three items), and environment (eight items). There are two additional questions on overall health-related quality of life and general health. Each question is rated on a 5-point Likert interval scale ranging from 1 (poor) to 5 (good). At the end, scores for each question and a mean score computed for each domain are reported. To further investigate psychosocial outcomes, the *Beck Depression Inventory* [95], the *Beck Anxiety Inventory* [96], and the *Psychological General Well-Being Index* are used [97-99]. The *Beck Depression Inventory* and the *Beck Anxiety Inventory* are each comprised of 21 groups of statements that are evaluated on 4-point Likert scales, with higher scores indicating higher depressive or anxiety-related symptoms, respectively. The *Psychological General Well-Being Index* includes 22 items organized around components of psychological well-being, such as anxiety, positive well-being, self-control, depression, and general health and vitality. Response options for each item are individualized according to the given affective experience. Intensity or frequency of experience during the past month is rated on a 6-point Likert scale ranging from 0 (most negative option) to 5 (most positive option).

Participant Satisfaction and Perspectives

For participant satisfaction, an updated version of the *Montreal Walking Exoskeleton Satisfaction and Perspectives Questionnaire* (MWESP-Q) is completed online at T_2. This questionnaire includes 54 statements that are organized around seven key domains: overall satisfaction related to the training program (two statements); satisfaction related to the overground robotic exoskeleton (seven statements); perceived learnability (12 statements); satisfaction related to the program attributes (eight statements); perceived health benefits (12 statements), including sentences that relate to pain, spasticity, bowel functions, and sleep; perceived risks and fears (11 statements); and perceived motivation to engage in regular physical activity (two statements). Each statement is rated using a 7-point Likert scale ranging from 1 (most negative option; eg, strongly disagree) to 7 (most positive option; eg, strongly agree) [64].

For participants' perspectives, a 20-30-minute semistructured interview is conducted over the phone to capture their general experience when participating in the wearable robotic exoskeleton–assisted training program. The interviews also serve as a platform for documenting participants' perspectives on the future of wearable robotic exoskeleton technology. To do so, various themes are discussed: potential benefits and recommendations for wearable robotic exoskeleton–assisted walking during the acute and subacute phases following spinal cord injury (eg, timing and conditions) or in a clinical setting during the chronic phase; opportunities for improvement (eg, functionality and structural aspects of the wearable robotic exoskeleton); and recommendations for a future home- or community-based wearable robotic exoskeleton–assisted walking program (eg, stairs, different surfaces, donning and doffing the wearable robotic exoskeleton without assistance, and operating the wearable robotic exoskeleton without assistance). The research professional who conducts these interviews has never met the participants and is not a member of the research team. All interviews are recorded to later enable verbatim transcription.

Statistics

Sample Size Estimation

The sample size estimate was based on a comparison using the variability of the absolute change (ie, mean ±SD) in both body composition and bone mineral density (ie, main outcomes) measured pre- and postintervention in our preliminary study [61] and computed with a computerized sample size calculator [100]. Considering the self-controlled design of the study, a total of 18 participants are required to have an 80% chance of detecting a significant increase at the 5% level in the leg lean body mass (kg) at the tibia measured by DXA from 14.0 to 15.8 ±2 mg/cm^3 [61]. Likewise, a total of 18 participants are required to have an 80% chance of detecting a significant increase at the 5% level in the bone mineral density (mg/cm^3) at the tibia measured by pQCT from 466 to 532 ±70 mg/cm^3 [61]. Considering the dropout rate of 7.1% found during the feasibility study [46], an additional 2 participants were added for a total sample size of 20 participants.

Quantitative and Qualitative Analyses

Descriptive statistics (eg, mean, SD, and 95% confidence interval) will be calculated for data summarizing sociodemographic characteristics as well as clinical and laboratory outcomes collected at the different measurement times. The normality of all data distributions and the absence of outliers will be verified via the Shapiro-Wilk test of normality and the absence of studentized residuals greater than ±3 SDs, respectively. Whenever applicable, the level of significance will be set at P≤.05 for all statistical tests and the data will be analyzed using SPSS, version 25.0 (IBM Corp).

For Hypothesis 1, one-way analysis of variance for repeated measures (ie, normally distributed continuous data) or Freidman

tests (ie, non-normally distributed continuous or categorical data) with planned comparisons based on the hypothesis and Bonferroni correction will be conducted to detect significant time effects, with a special interest for the preintervention (T_0 vs T_1), intervention (T_1 vs T_2), and retention (T_2 vs T_3) phases. In accordance with the principles of a classic intention-to-treat approach, all participants will be included in the final analyses, regardless of withdrawal, compliance, or unintentional missing data. For missing data, imputation of the mean value for the specific group at the specific assessment time will be used. Per-protocol exploratory analyses will also be performed comparing outcomes for those with walking program compliances of greater than 75% to examine maximum treatment efficacy.

For Hypotheses 2 and 3, Pearson or Spearman correlation coefficients will investigate the strength and direction of the relationships between the overall observed changes ($[T_1–T_2] / T_1 \times 100$) for each personal factor (ie, dependent variable) and the program characteristics (ie, independent variable). Independent variables having reached a critical threshold ($P \leq .25$) will then be confronted in a stepwise multiple linear regression analysis to identify the three best predictors for each dependent variable and the coefficient of determination (R^2) of the model. To determine the factors for identifying the best responders to the program, analyses similar to the previous ones will be completed, except that the independent variables will be sociodemographic characteristics, anthropometric parameters, characteristics of the SCI, personal factors, and functional disability.

For Hypothesis 4, using Microsoft Excel, descriptive statistics of the 54 statements (ie, mean, median, and SD) will summarize the results of the satisfaction survey (ie, the MWESP-Q). Audio recordings of the interviews will be transcribed verbatim using Microsoft Word. A summer research intern will read the transcripts and generate initial codes or subthemes. A co-codification of the first transcript will be done manually on printed paper with the list of initial codes and subthemes; this will be done independently by three research collaborators (ie, a summer research intern, a doctoral student, and a researcher who is a member of the research team). They will write codes directly in the margin of the printed transcripts. They will then meet via audio and video conferencing to compare and review coding, discuss discrepancies, and modify codes if necessary. This process will be done twice with the transcripts of the first two participants. To start the computerized qualitative analysis, all transcripts will be interpreted using thematic content analysis, where narrative data will be thematically coded and appraised using NVivo 10 (QSR International). A final report, integrating findings from the MWESP-Q and the interviews, will be produced and recommendations will be incorporated in order to shape the development of a future home- or community-based adapted physical activity program.

Results

This study was recently initiated at the *Laboratoire de pathokinésiologie* of the Centre de recherche interdisciplinaire en réadaptation du Montréal métropolitain (CRIR), Québec, Canada, which is part of the Centre intégré universitaire de santé et de services sociaux du Centre-Sud-de-l'Ile-de-Montréal in Montreal, Canada, and at the *Laboratoire du muscle et de sa fonction* of the Université du Québec à Montréal. This project received ethical approval on March 14, 2019, from the CRIR ethics committee and was registered on June 7, 2019, with the US National Library of Medicine at ClinicalTrials.gov (NCT03989752). This study is expected to be completed by spring 2021, with results to follow shortly after.

Discussion

Overview

This project innovates by being among the first studies to comprehensively, prospectively, and longitudinally investigate the effects of a wearable robotic exoskeleton–assisted walking program among long-term WU_{SCI} who have a very poor prognosis for walking recovery [101]. This study investigates the effects on organic systems, functional capacities, and multifaceted psychosocial factors. This study also investigates the influence of walking program attributes (eg, duration, training frequency, and intensity) on these effects. This project is crucial in strengthening evidence in this field based on hierarchical forms of knowledge creation. This project is also timely, since WU_{SCI} are now requesting the democratization of accessibility to this technology during rehabilitation and in the community at a faster rate than evidence is generated and shared with physical activity and rehabilitation professionals, administrators, and policy makers. Strengthened evidence is urgently needed to fill this knowledge gap to some extent and to start informing the decision-making process of these stakeholders regarding the possibility of purchasing wearable robotic exoskeletons as well as developing, implementing, and evaluating activity-based and adapted physical activity programs with wearable robotic exoskeletons in clinical practice (eg, walking program). Moreover, this evidence, once coupled with clients' perspectives, may become key precursors to (1) develop and implement community- and/or home-based walking programs, (2) advocate for policy changes to broaden accessibility to wearable robotic exoskeletons, and (3) propel future larger-scale pragmatic or randomized controlled trials with an appropriate comparator targeting the effectiveness of walking programs with a wearable robotic exoskeleton. Of even greater relevance, it is expected that walking programs with a wearable robotic exoskeleton will reduce impairments (ie, organic systems) and optimize aptitudes, which are expected to positively influence psychosocial outcomes in WU_{SCI} and potentially those with other sensorimotor impairments (eg, stroke). In the long term, although not measured in the proposed study, we can hypothesize that indirect societal benefits may become tangible via reduced caregiver burden and reduced health care costs, for example. By optimizing their global health, especially as they age, WU_{SCI} will also remain in a *state of readiness* to benefit from future advances in neural repair, recovery, or rehabilitation technology. Lastly, as some wearable robotic exoskeletons may become approved for home or community use by Health Canada, some WU_{SCI} are now

envisioning their use as personal neuroprostheses for ambulation in their daily lives as a complement to wheelchair mobility in the near future. Still, strengthened evidence is needed to support the prescription and reimbursement processes in order to accelerate uptake of wearable robotic exoskeletons in the community.

Many stakeholders may benefit from this interventional study. For WU_{SCI} who have no or very limited walking ability, the walking program with the wearable robotic exoskeleton is not expected to have any reversal effect on their walking capacity without this novel mobility assistive technology. However, this project is relevant since it will generate the first evidence of the anticipated cardiorespiratory, musculoskeletal, and endocrine-metabolic health adaptations upon completion of a walking program with a wearable robotic exoskeleton. For the first time, the extent to which these adaptations translate into beneficial effects on functional capacity will also be verified, as will their effects on health-related quality of life and psychological health. This includes the psychological well-being domain, which was not specifically measured during the feasibility study but was mentioned by the majority of participants. Given the fact that the population of WU_{SCI} continues to grow and that they now live longer, these potential beneficial effects are further warranted. The caregiver burden and the potentially costly long-term expenditures associated with adverse health events may also decrease. For rehabilitation professionals, the proposed project is relevant since strengthened evidence regarding the effects of the walking program and the characteristics of the best responders will be generated and will inform clinical decision-making processes or the development of a clinical algorithm for referring individuals with SCIs to a walking program. For rehabilitation program administrators and policy makers, the proposed study is relevant since the evidence generated may further confirm the need for publicly funded clinical and technological infrastructures to create structured programs incorporating walking technologies, such as the wearable robotic exoskeleton, and outcome measures into rehabilitation or adapted physical activity centers. Both program administrators and policy makers will need to work collaboratively and cohesively to develop creative solutions to address this current service gap and engage in transformative improvements. For the research community, this project provides a unique opportunity to create a strong multidisciplinary team of well-established scientists with diverse and complementary academic training as well as clinical and fundamental research expertise. For manufacturers with an interest in wearable robotic exoskeletons, among others, this project is relevant since the input from powered exoskeleton end users (ie, WU_{SCI}) will become available and may enrich the continuous quality improvement process. This process is imperative to further support and accelerate the development of wearable robotic exoskeletons and to reach key commercialization milestones for the technology to become personalized and accessible for WU_{SCI} interested in home or community use (ie, neuroprosthesis) in the next decade.

Potential Challenges and Appropriate Mitigation Strategies

A few potential challenges merit attention:

1. Some potential participants will have insufficient passive range of motion at the lower extremities to engage with the project. These participants will be provided with a 4- to 6-week home-based stretching program, will be reassessed, and may become eligible later.
2. Female WU_{SCI} may be underrepresented. Efforts will be made for the sample to be representative of the SCI population and to have women make up 20% of the sample. However, since the minority of individuals affected by SCIs are female and the sample size is limited (n=20), it is unlikely that statistical analysis by subgroups (ie, male vs female) will be feasible in order to account for potential sex and gender differences. Nonetheless, descriptive statistics will present results separately for women and men whenever indicated.
3. A small number of participants may demonstrate vitamin D deficiencies [102]. To mitigate this risk, at T_0, the equivalent of 1 year of vitamin D3 supplementation will be provided to all participants who are not currently taking supplements. Moreover, all participants will be instructed on healthy balanced diets.
4. Some participants may concurrently engage in extraneous physical activity or may seek cointerventions during the project. Participants will be asked to maintain their customary level of physical activity during the project and to avoid engaging in new cointerventions. Any unintended intervention (ie, contamination or cointervention) that may influence the results will be documented and its effect carefully verified by the research team and possibly considered as a dichotomous variable (ie, present vs absent).
5. Some participants may experience some lower extremity neurorecovery. In the event a participant was to experience neurorecovery (ie, lower extremity motor score of ≥20 on the American Spinal Injury Association Impairment Scale), he or she would be withdrawn from the project and referred for a comprehensive neurological assessment and to an advanced locomotor training program.

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Conflicts of Interest

None declared.

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Abbreviations

aBMD: areal bone mineral density

CRIR: Centre de recherche interdisciplinaire en réadaptation du Montréal métropolitain
DXA: dual-energy x-ray absorptiometry
MWESP-Q: Montreal Walking Exoskeleton Satisfaction and Perspectives Questionnaire
pQCT: peripheral quantitative computed tomography
SCI: spinal cord injury
T_0: control measurement time
T_1: preintervention measurement time
T_2: postintervention measurement time
T_3: retention measurement time
vBMD: volumetric bone mineral density
WU_{SCI}: wheelchair users with a chronic spinal cord injury

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Protocol

Chronic Kidney Disease in Tasmania: Protocol for a Data Linkage Study

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Abstract

Background: Chronic kidney disease (CKD) is a significant and growing health burden globally. Tasmania has the highest state prevalence for non-Indigenous Australians and it has consistently had the lowest incidence and prevalence of dialysis in Australia.

Objective: To examine the gap between the high community prevalence of CKD in Tasmania and the low use of dialysis.

Methods: This is a retrospective cohort study using linked data from 5 health and 2 pathology data sets from the island state of Tasmania, Australia. The study population consists of any person (all ages including children) who had a blood measurement of creatinine with the included pathology providers between January 1, 2004, and December 31, 2017. This study population (N=460,737) includes within it a CKD cohort, which was detected via pathology or documentation of kidney replacement therapy (KRT; dialysis or kidney transplant). Kidney function (estimated glomerular filtration rate [eGFR]) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Individuals with 2 measures of eGFR<60 mL/min/1.73 m^2, at least 90 days apart, were identified as having CKD and were included in the CKD cohort. Individuals treated with dialysis or transplant were identified from the Australia and New Zealand Dialysis and Transplant Registry.

Results: The study population consisted of 460,737 people (n=245,573 [53.30%] female, mean age 47.4 years) who were Tasmanian residents aged 18 years and older and were followed for a median of 7.8 years. During the later 5 years of the study period, 86.79% (355,622/409,729) of Tasmanian adults were represented. The CKD cohort consisted of 56,438 people (ie, 12.25% of the study population; 53.87% (30,405/56,438) female, mean age 69.9 years) followed for a median of 10.4 years with 56,039 detected via eGFR and 399 people detected via documentation of KRT. Approximately half (227,433/460,737, 49.36%) of the study population and the majority of the CKD cohort (41,448/56,438, 73.44%) had an admission episode. Of the 55,366 deaths recorded in the study population, 45.10% (24,970/55,366) had CKD.

Conclusions: Whole-of-population approaches to examine CKD in the community can be achieved by data linkage. Over this 14-year period, CKD affected 12.25% (56,438/460,737) of Tasmanian adult residents and was present in 45.10% (24,970/55,366) of deaths.

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KEYWORDS

chronic kidney disease; dialysis; transplantation; data linkage.

Introduction

Chronic kidney disease (CKD) is a significant and growing public health burden that manifests in substantial burden of illness and premature mortality [1]. It has been named one of the "most neglected chronic diseases" [2] and has a complex interaction with other conditions, serving as a multiplier of risk in all populations. CKD significantly increases the underlying risk of premature death, hospitalization, cancer, diabetes, or major vascular events by twofold to fivefold [2]. In 2012, the total costs attributable to CKD in Australia were estimated at AUD 4.1 billion (US $3 billion) [3]. Even early stage CKD is associated with a 50% increase in health-related expenditure; with later stages this is a sixfold increase [3]. Much of this cost is associated with the use of kidney replacement therapy (KRT; dialysis or kidney transplants).

Tasmania is the island state of Australia with a population of half a million people spread over 68,000 km^2. The whole of Tasmania is classified as rural or remote with many people (37%) living in areas of high disadvantage. The median age is 42 years, which is 5 years older than the median for Australia [4]. A significant proportion of the Tasmanian population is known to have CKD [5] with Tasmania having the highest state prevalence of CKD (highest prevalence of estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2 and the highest prevalence of albuminuria) [6] among non-Indigenous Australians. Conversely, Tasmania has the lowest incidence of uptake of dialysis and transplant (87 per million population [pmp] compared with 124 pmp nationally) and the lowest prevalence of dialysis (400 pmp compared with 536 pmp nationally) [7,8]. Currently, the reasons for this gap between high community prevalence of CKD and low use of dialysis remain unknown. Dialysis use in all Australian states is funded by the government and therefore decisions on its use are not directly influenced by cost to the dialysis patient. Despite this model, dialysis prevalence ranges from 2956 pmp in the Northern Territory down to 400 pmp in Tasmania, likely influenced by local population characteristics and treatment pathways.

Linking routinely collected health data, pathology, and registry data, we examine the gap between the high community prevalence of CKD in Tasmania and the low use of dialysis. We hypothesize that many Tasmanians with CKD will (1) have a slow decline in kidney function (eGFR), (2) experience multiple comorbidities, (3) have a higher mortality rate than those without CKD, and (4) have limited access to tertiary health services depending on their rurality and socioeconomic status.

Specific aims of this data linkage study are to (1) confirm the Tasmanian burden of CKD; (2) identify geographic, gender, and age-related variation in CKD burden, progression, and use of dialysis; (3) report the mortality rate and survival of Tasmanians with CKD; (4) examine how quickly kidney function deteriorates; (5) report the general health burden of Tasmanians with CKD including diabetes, hyperlipidemia, cancer, and cardiovascular disease.

This will give us better quantitative information about the detection and progression of CKD in Tasmanians, allowing us to better understand this gap and identify health service and community needs for better management of CKD in Tasmania.

Methods

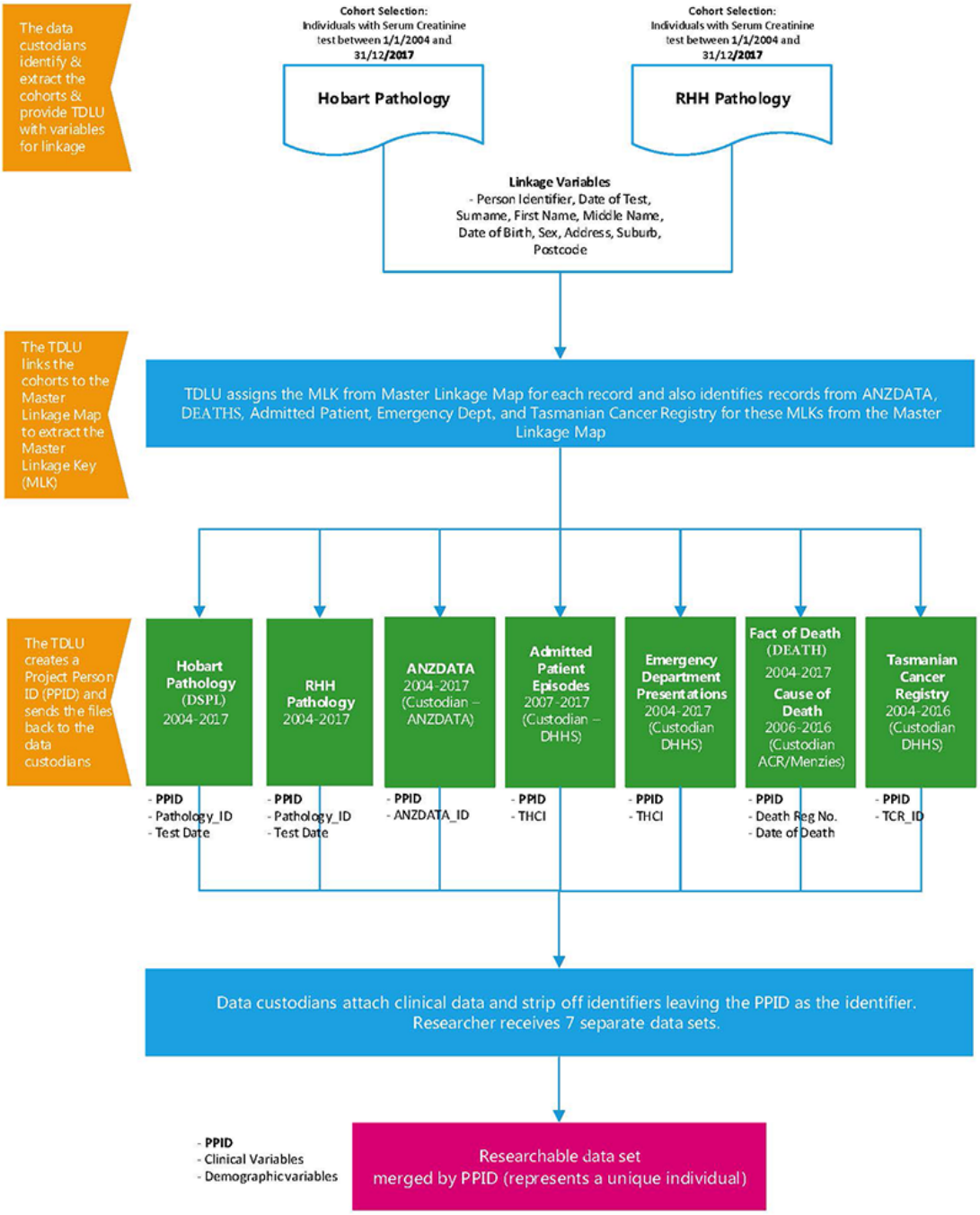
Overview

This is a retrospective cohort study using linked data from 2 pathology providers and 5 administrative health data sets, from January 1, 2004, to December 31, 2017, 14 years in total, in the Australian state of Tasmania, an area of 68,400 km^2 with approximately 510,000 people [9].

Data Sets for Linkage

Ethical approval was granted by the Tasmanian Health and Medical Human Research Ethics Committee (project H0016499, approval date June 26, 2017) to access and link the following data sets (Figure 1):

Figure 1. Linkage map.



- Community and Hospital Pathology (Diagnostic Services Pty Ltd [DSPL]): Hobart Pathology, Launceston Pathology, and North-West Pathology. Pathology records provided included date, eGFR, urinary albumin-to-creatinine ratio, measures of diabetes (HbA1C), cholesterol, etc.
- Royal Hobart Hospital Pathology (RHHPATH): The largest Tasmanian public hospital pathology service provider. The data set includes pathology results for both community and hospitalized Tasmanians. Pathology records provided are the same as Community Pathology (above).
- Australia and New Zealand Dialysis and Transplant Registry (ANZDATA): records on all Tasmanians treated with dialysis or kidney transplant including the cause of kidney disease and details of their dialysis or transplant.
- Public Hospital Admitted Patient data set: date, admission, discharge, and clinical variables including primary and related diagnoses by ICD-10 code (10th edition of International Classification of Diseases and related health problems) and classification by the Australian Refined Diagnosis-Related Group for episode costing.
- Public Hospital Emergency Department Presentations: date, episode, discharge, and clinical variables including diagnoses and urgency-related groups for costing.
- Tasmanian Cancer Registry (TCR): clinical information including date, type, and stage of cancer.
- Tasmanian Fact of Death (DEATH): date of death from Births, Deaths and Marriages Tasmania; and Tasmanian Cause of Death, which presents both coded underlying and

contributing cause of death from the Australian Coordinating Registry.

Study Population

This retrospective cohort study consists of an overall study population cohort that includes within it a CKD cohort, consisting of an eGFR cohort and a KRT cohort.

The study population consists of any adult (aged 18 years and older) who had a blood measurement of creatinine with either pathology provider, RHHPATH or DSPL, between January 1, 2004, and December 31, 2017. These providers provide the majority of community pathology services to Southern, Northern, North-West, and West of Tasmania and provide inpatient pathology services to public and private hospitals in both the south and north-west. We were unable to obtain pathology results from Launceston General Hospital or smaller Tasmanian private pathology providers. We then identified people as being Tasmanian by comparing the recorded postcode on pathology report at the date of creatinine measurement against known Tasmanian Statistical Areas Level 2 (SA2).

The eGFR cohort is identified from within the study population, where a patient has 2 recorded eGFR < 60 mL/min/1.73 m^2, at least 90 days apart [10], but no more than 3 years apart. We then added to this people identified in the KRT cohort (below) to comprise the CKD cohort.

The KRT cohort is identified from within the study population using ANZDATA [7,8]. This registry was established in 1963 and maintains records of all patients with end-stage kidney disease (ESKD) receiving dialysis or transplantation in Australia and New Zealand. All patients residing in Tasmania receiving ESKD treatment and recorded in ANZDATA between January 1, 2004, and December 31, 2017, who had blood creatinine measured in the study period from the pathology providers above, are included in the KRT cohort.

Data Linkage

All linkage was performed by the Tasmanian Data Linkage Unit (TDLU), based at the Menzies Institute for Medical Research, University of Tasmania. The TDLU utilizes probabilistic record linkage using specialized data linkage software. This process attempts to link pairs of records based on the probability of them belonging to the same individual. The technique assigns scores based upon the agreement or disagreement of various linkage fields, and based upon the total score, record pairs are classified as either *matches* or *nonmatches*. The matches are recorded in the TDLU's Master Linkage Map. A series of Structured Query Language (SQL) queries are executed against the Master Linkage Map to check for incorrect links (false positives) and missed links (false negatives).

The TDLU uses a combination of linkage fields including source system identifier; first name, middle name, and surname; date of birth and date of death; gender; street address; suburb; and postcode. Blocking strategies (only matched pairs that meet certain basic criteria) are used to make the linkage process more efficient. In order for two individuals to be compared, they must have matching values for one or more blocking variables. The TDLU currently blocks on surname, street address, date of birth, derived postcode/month of birth variable. A process of deduplication is applied to data sets prior to linkage. This process identifies duplicate records within one data set using specified linkage variables.

After linkage of 2 or more data sets is completed, a process of clerical review is conducted. This ensures records that reach the score threshold, and are linked, are true matches. Only those pairs of records where there is at least one mismatch, based on either first name, surname, date of birth, date of death, or sex, between the newly linked record and the remaining records in the group are reviewed. This is known as the *review pool* (pool). The first stage of clerical review is to review all the groups in the *pool* where the linkage system has combined 3 or more groups of individuals (2 or more groups from the existing Master Linkage Map and the new record being linked). This situation occurs where there are 2 or more existing groups that are potential matches for the new record. In the majority of cases, the new record will become part of an existing group. There are a small number of cases where the new record contains information that allows 2 previously distinct groups to be merged into 1 group.

The second stage of the clerical review process selects groups from the *pool* where the new record has been linked with only 1 existing group from the Master Linkage Map. Groups are reviewed based on the scores of the new record to other records within the group. Groups with low scores are clerically reviewed first to check for false positives. Reviewers then work upward through the scores until no further false positives are identified. Following this stage of review, a further round of quality assurance is conducted to ensure the linked data satisfy a range of logic checks. These checks aim to identify and correct false positives (where 2 individuals have been incorrectly linked) and false negatives (where records for the same individual have not been linked).

On successful linkage, each individual identified was assigned a project person identifier (PPID). There were 521,320 PPIDs generated during data linkage (Table 1).

Table 1. Linkage matrix: number of individuals identified in each data set.

	DSPL[a] pathology[b]	RHH[c] pathology[b]	ANZDATA[b,d]	Admitted patient[e]	Emergency department[b]	Tasmanian Cancer Registry[f]	DEATHS[b,g]
DSPL pathology[b]	*490,026*[h]	123,191	1098	237,122	315,293	41,764	53,364
RHH pathology[b]	123,191	*154,485*	835	106,827	125,038	19,065	26,171
ANZDATA[b]	1098	835	*1214*	998	1060	184	480
Admitted patient[e]	237,122	106,827	998	*253,036*	221,297	30,535	38,234
Emergency department[b]	315,293	125,038	1060	221,297	*337,914*	31,062	46,422
Tasmanian Cancer Registry[f]	41,764	19,065	184	30,535	31,062	*42,467*	18,209
DEATHS[b]	53,364	26,171	480	38,234	46,422	18,209	*55,366*

[a]DSPL: Diagnostic Services Pty Ltd.

[b]January 1, 2004, to December 31, 2017.

[c]RHH: Royal Hobart Hospital.

[d]ANZDATA: Australia and New Zealand Dialysis and Transplant Registry.

[e]January 1, 2007, to December 31, 2017.

[f]January 1, 2004, to December 31, 2016.

[g]DEATHS: Births, Deaths and Marriages Tasmania (Fact of Death).

[h]Italics indicate where data sets align.

Geocoding

The TDLU, in partnership with the Menzies Institute for Medical Research, has developed a geocoding module to enable the derivation of latitude and longitude for large unit record data sets. The module uses fuzzy matching to link address data to the Geocoded National Address File. After processing, the system allocates a latitude and longitude at unit record level based on the following geographic levels:

- Address: Records coded to the *Address* level have been found as an exact match in the database and matched on street number, street name, suburb, state, and postcode.
- Street: Records coded at the *Street* level have been matched on street name and suburb, but the street number could not be found. Records have been coded to the midpoint of the street.
- Locality: Records coded at the *Locality* level have been matched on suburb, state, and postcode only. Records have been coded to the midpoint of the matching suburb.
- PO Box: These represent records geocoded to the Locality of the PO Box address.
- None: These records relate to addresses that could not be found in the database or Google Maps.
- Manual: These records have been found manually in Google Maps through a clerical review module and had their latitude and longitude recorded manually.

Once a latitude and longitude have been assigned, the system assigns a *meshblock* (defined as a geographic area) code to enable structures from the Australian Statistical Geography Standard to be derived. Statistical areas ranging from SA1 to SA4, as well as other Australian Bureau of Statistics geographic structures, can be produced using this system. Given the small population size and the potential for identification, we restricted the coding to SA2 and above (population areas of >5000 people).

Data Cleaning

Access, cleaning, and analysis of the linked data set were limited to 2 authors (AK and TS). In order to calculate eGFR from serum creatinine (SCr) results, each PPID requires documentation of gender (binary classification: male or female). The PPID gender was accepted if it was recorded consistently in each data set on every administrative record or if the majority of data sets had gender recorded as a specific gender. The PPID gender was left as *unknown* if it was recorded as unknown in all available data sets or was ambiguous between administrative data sets. If no gender could be determined, the pathology records were removed from the data set. There were 357 individuals of the total PPIDs generated during data linkage (521,320, 0.07%), with gender not recorded as male or female.

Detection of CKD via Pathology (eGFR Cohort)

SCr result was used to calculate eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [11,12]. Tasmanian laboratories use enzymatic assays for

measurement of creatinine and all results are isotope dilution mass spectrometry aligned as previously reported [13]. Stages of CKD were classified based on first eGFR according to National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines [10] and include stage 1 (eGFR≥90 mL/min/1.73 m^2), stage 2 (eGFR=60-89 mL/min/1.73 m^2), stage 3a (eGFR=45-59 mL/min/1.73 m^2), stage 3b (eGFR=30-44 mL/min/1.73 m^2), stage 4 (eGFR=15-29 mL/min/1.73 m^2), and stage 5 (eGFR<15 mL/min/1.73 m^2 or treated with dialysis or a transplant).

The following CKD-EPI formulae were used:

- For females with SCr ≤62 µmol/L: eGFR (mL/min/1.73 m^2)=144×(SCr in µmol/L × 0.0113/0.7)$^{-0.329}$× (0.993)$^{\text{age in years}}$
- For females with SCr >62 µmol/L: eGFR (mL/min/1.73 m^2)=144 × (SCr in µmol/L × 0.0113/0.7) $^{-1.209}$ × (0.993)$^{\text{age in years}}$
- For males with SCr ≤80 µmol/L: eGFR (mL/min/1.73 m^2)=141 × (SCr in µmol/L × 0.0113/0.9)$^{-0.411}$ × (0.993)$^{\text{age in years}}$
- For males with SCr >80 µmol/L: eGFR (mL/min/1.73 m^2)=141 × (SCr in µmol/L × 0.0113/0.9)$^{-1.209}$× (0.993)$^{\text{age in years}}$

The method to identify CKD consists of the following (simplified) steps:

1. Calculation of eGFR (CKD-EPI) from SCr for each pathology result in the study population.
2. Identification of CKD-qualifying eGFR results by filtering to include only results where eGFR is <60 mL/min/1.73 m^2 and PPID age at result ≥18 years.
3. Calculation of the number of days between qualifying eGFR results (eGFR < 60 mL/min/1.73 m^2 on at least two occasions).
4. Search for a qualifying eGFR result date greater than 90 days since a previous qualifying result date, but no more than 3 years since a previous qualifying result date.
5. If a second qualifying result date was detected between 90 days and 3 years, the date of the second qualifying result was deemed to be date of diagnosis.
6. PPID was identified as Tasmanian if they had at least one Tasmanian SA2 recorded in pathology.

There were 56,039 Tasmanian PPIDs diagnosed with CKD via pathology.

Identifying CKD via ANZDATA Registry (KRT Cohort)

Although all people treated with dialysis or transplant are classified as having CKD, the pathology method described above may not identify someone who has had a successful kidney transplant and an eGFR >60 mL/min/m^2. Therefore the ANZDATA registry was checked for PPIDs that were not detected via the pathology detection method and had at least one treatment center within Tasmania or had received a transplant.

There were 399 Tasmanian PPIDs detected via their presence within the ANZDATA registry, due to one or more of the following: (1) PPID entry being prior to start of the pathology data set (ie, before January 1, 2004); (2) PPID having insufficient pathology results within the pathology data set prior to entry to ANZDATA; (3) PPID entry to ANZDATA prior to age 18, and subsequently reaching the age of 18 in later years; and (4) PPID had a transplant and a Tasmanian SA2 coded pathology data after date of entry to ANZDATA.

CKD Cohort

We combined the PPIDs from both methods of detection to create a CKD cohort. In addition to PPID and sex, the following variables were extracted and added to the CKD cohort data set: Age at detection, Date at detection, Date of pathology or Date of entry to ANZDATA, Method of detection, eGFR CKD-EPI at detection, CKD Stage at detection, and SA2 at detection.

For the PPIDs that were present in ANZDATA, the following additional variables were added: Age at entry to registry, Date of entry to registry, eGFR CKD-EPI at entry to registry, Date of first dialysis, Age at first dialysis, Date of first transplant (if applicable), and Age at first transplant (if applicable)

Pathology Variables Obtained

In addition to creatinine, we obtained 25 other pathology variables (Multimedia Appendix 1). If PPIDs had an SCr test during the study period, we received all requested pathology data for them, regardless of if they had an SCr test on the same day or not.

Identifying Cause of CKD and Comorbidities

The cause of CKD was identified (where available) from the admitted patient data set using ICD-10 codes (Multimedia Appendix 2) and ANZDATA using primary renal disease code.

Comorbidities of interest were identified using ICD-10AM codes for diabetes (ICD-10AM codes E10-14), cardiovascular disease (ICD-10AM codes I00-99), and cancer (ICD-10AM codes C00-D48). Other comorbidities were determined using both the Charlson Comorbidity Index [14] and Elixhauser Comorbidity Index [15].

Identifying Cause of Death

Death data are recorded in multiple data sets including DEATH, TCR, Admitted Patient, and ANZDATA. DEATH (fact of death) was used as the primary data source, with additional death dates and cause of death added from additional data sets. Specific kidney disease–related cause of death was identified using the Australian Institute of Health and Welfare report, “Deaths from Chronic Kidney Disease” [16].

Results

Study Population

The linkage identified 521,320 people who had an SCr test in Tasmania during the 14-year study period, of whom 460,737 were determined to be Tasmanian residents (at the time of

pathology test) aged 18 years or older and therefore became *the study population*.

For the 5-year period (2013-2017) there were 355,622 unique individuals aged 18 years and older included in our linked data set. As the estimated adult resident population in Tasmania was 409,729 at this time, we estimate that our study population represents approximately 86.79% of Tasmania's resident adult population during this 5-year period (Table 2).

The study population showed significant variation by age (Figure 2A and 2B), with the older population (aged 60 years and older) more likely to have a pathology test in this 5-year period (P<.001).

There were 460,737 people in the study population, of which 53.30% (245,573/460,737) were female with a mean age of 47.4 (SD 18.3) years, having 1.1 creatinine results per person per year over the 7.8 (interquartile range [IQR] 8.3) years of follow-up (Table 3).

Table 2. The number of unique individuals and proportion of Tasmania's adult population included in the data set in the previous 1, 2, 3, or 5 years (% of estimated resident population [9] aged 18 years and older [ERP[a] 18+]).

	Unique PPID[a]				Population (ERP 18+[b])	Unique PPID % of ERP			
Year	1 year	2 years	3 years	5 years		1 year	2 years	3 years	5 years
2004	99,338	99,338	99,338	99,338	365,597	27.17	27.17	27.17	27.17
2005	109,184	157,570	157,570	157,570	369,271	29.57	42.67	42.67	42.67
2006	116,784	168,977	200,422	200,422	372,707	31.33	45.34	53.77	53.77
2007	126,803	180,495	213,435	236,465	376,512	33.68	47.94	56.69	62.80
2008	140,792	195,704	228,096	269,775	381,317	36.92	51.32	59.82	70.75
2009	149,900	209,638	242,501	284,069	386,739	38.76	54.21	62.70	73.45
2010	158,645	220,167	255,302	296,769	391,666	40.50	56.21	65.18	75.77
2011	169,235	232,304	267,756	310,200	395,228	42.82	58.78	67.75	78.49
2012	176,243	242,159	278,154	321,985	396,592	44.44	61.06	70.14	81.18
2013	183,440	250,054	287,543	332,048	397,807	46.11	62.86	72.28	83.47
2014	182,994	254,351	292,988	339,409	399,987	45.75	63.59	73.25	84.86
2015	184,173	254,519	295,896	345,153	402,512	45.76	63.23	73.51	85.75
2016	189,409	258,280	298,855	350,375	405,167	46.75	63.73	73.76	86.48
2017	195,114	265,153	304,058	355,622	409,729	47.62	64.71	74.21	86.79

[a]ERP: estimated resident population.

[b]PPID: project person identifier.

Figure 2. (a) Male unique PPIDs by age group per year (% of Tasmanian Population). (b) Female unique PPIDs by age group per year (% of Tasmanian Population).

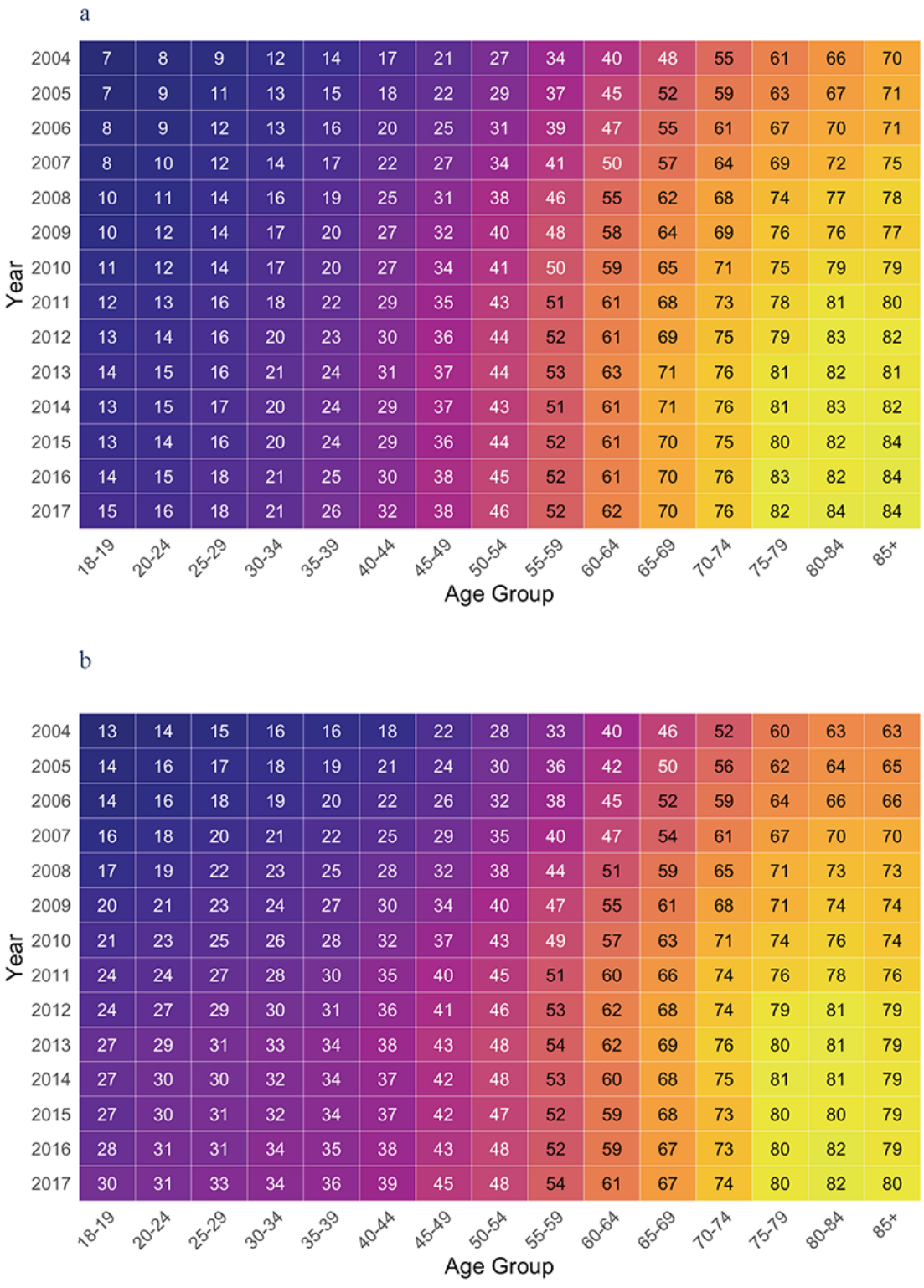


Table 3. Study demographics.[a]

Demographics	Study population	CKD[b] cohort	Pathology	ANZDATA[c]
Number of individuals (18 years and older)	460,737	56,438	56,039	399
Age (years) at initial eGFR[d], mean (SD)	47.4 (18.3)	69.7 (11.8)	69.9 (11.7)	51.2 (15.5)
Female, n/N (%)	245,573/460,737 (53.30)	30,405/56,438 (53.87)	30,267/56,039 (54.01)	150/399 (37.59)
Follow-up (years), median (IQR)	7.8 (8.3)	10.4 (6.2)	10.4 (6.2)	9.2 (9.8)
Creatinine tests per person per year, median (IQR)	1.1 (2)	2.4 (2.8)	2.4 (2.8)	9.9 (10.6)
Age (years) at death, mean (SD)	77.4 (13.9)	82.8 (9.7)	83 (9.5)	64.9 (12.5)
Number of deaths	55,366	24,970	24,777	193
PPID[e] (%) with an admission	227,433 (49.36)	41,448 (73.44)	41,130 (73.40)	318 (79.70)
Total number of admissions	1,319,293	456,337	387,619	68,718
Admissions per person per year, median (IQR)	0.9 (4.1)	3.4 (46.8)	1.9 (24.2)	88.8 (79.3)
PPID (%) with emergency department presentation	295,943 (64.23)	44,801 (79.38)	44,441 (79.30)	360 (90.23)
Total number of emergency department presentations	1,470,819	261,603	258,343	3260
Emergency department presentations per person per year, median (IQR)	0.9 (1.5)	0.9 (1.3)	0.9 (1.3)	1.7 (2)
PPID (%) with cancer	42,099 (9.14)	12,975 (22.99)	12,906 (23.03)	69 (17.29)
eGFR (mL/min/1.73 m^2), mean (SD)	83.9 (29.4)	56.6 (23.2)	57.1 (22.9)	33.7 (28.8)
uACR[f] (mg/mmol), mean (SD)	13.4 (77)	26.4 (93.6)	25.5 (91.6)	50.4 (131.4)

[a]Admissions include same day and overnight.

[b]CKD: chronic kidney disease.

[c]ANZDATA: Australia and New Zealand Dialysis and Transplant Registry.

[d]eGFR: estimated glomerular filtration rate.

[e]PPID: project person identifier.

[f]uACR: urinary albumin-to-creatinine ratio.

CKD Cohort

The CKD cohort consisted of 56,438 people, of which 53.87% (30,405/56,438) were female with a mean age of 69.7 (SD 11.8) years and median follow-up of 10.4 (IQR 6.2) years. Stage of CKD (when first meeting the criteria for CKD in the data set) was stage 3a in 73.07% (41,242/56,438), stage 3b in 20.05% (11,315/56,438), stage 4 in 5.21% (2938/56,438), and stage 5 or on KRT in 1.67% (943/56,438).

KRT Cohort

The KRT cohort consisted of 399 people, of which there were 37.6% (150/399) of female with a mean age of 51.2 (SD 15.5) years. Follow-up of the KRT cohort was for a median of 9.2 (IQR 9.8) years.

Admissions and Comorbidities

Of the 460,737 people in the study population, 227,233 (49.32%) were in the Admitted Patient data set for a median of 1.0 (IQR 4.6) admissions per year. Of the 56,437 people in the CKD cohort, 41,448 (73.44%) were in the admitted data set for a median of 3.4 (IQR 46.8) admissions per year (Table 3), including same-day admissions for dialysis.

Deaths

During the 14-year study period there were 55,366 Tasmanian deaths recorded, of which 24,970 (45.10%) were in our CKD

cohort. Mean age of death in our CKD cohort was 84.1 (SD 9.6) years for women and 81.3 (SD 9.6) years for men.

Discussion

Overview of the Protocol

The aim of this study was to take a *whole-of-population* approach to identify and follow (through data linkage) Australians who develop CKD, and identify important outcomes such as hospital admission, dialysis use, kidney transplantation, cancer, or death. We identified 460,737 individuals who had a Tasmanian residential postcode recorded at the time of pathology collection and were aged 18 years and over. Of these, 56,438 (12.25%) met the KDIGO (Kidney Disease: Improving Global Outcomes) definition of CKD [10], making this the largest Australian CKD cohort yet reported.

The strengths of this data linkage project are the whole-of-population approach (an estimated 86.79% [355,622/409,729] of resident adult population included), longitudinal nature allowing adequate follow-up (median follow-up of CKD cohort of 10.4 years), and a relatively contained island population with a low population turnover [9]. In addition, we use biochemical measures rather than self-report to determine prevalence of CKD, diabetes, and hyperlipidemia and link to legislated data sets including the Births, Deaths and Marriages Tasmania Fact of death and the TCR. Our estimates of CKD prevalence are consistent with our previously published 2007 data [5] and the Australian Health Survey [6].

The quality and completeness of the administrative data sets included were variable, but data conflicts and missingness were proportionally small (no sex recorded for 0.07% [357/521,320] of PPIDs generated during data linkage). While ethnicity was recorded in several data sets, concordance was <90% and further work needs to be done to improve recognition and recording of diversity within these administrative data sets.

Notable limitations of our study include the lack of primary health data, prescribed medications including secondary prevention strategies, general information on health risk factors including actual weight, BMI, smoking history, or blood pressure control. In addition, we rely on coding practices across public health institutions for comorbidities. Private hospital admission data were not included, nor were admissions of Tasmanian residents who travel to other jurisdictions for management of these chronic conditions.

Throughout this study we have used KDIGO definitions of CKD stating that a person with 2 measurements of eGFR <60 mL/min/1.73 m^2 90 days apart has CKD. This definition does not separate kidney disease from kidney aging and therefore does not take into account the call for age-specific thresholds to allow for an age-adapted definition [17].

We have commenced the analysis of this linked data set and hope to report our findings to the Tasmanian community within 12 months. The results will give us better quantitative information about detection and progression of CKD in Tasmanians, areas and populations of high disease prevalence, and risk factors for CKD. This will allow us to better understand this gap and identify health service and community needs, to optimize management of CKD in Tasmania through early detection and treatment.

Conclusions

We have described our methodology for the largest (retrospective) Australian CKD cohort reported to date. We will use these linked data to estimate the burden of CKD in the Tasmanian community, the progression of CKD to ESKD, the presence and influence of coexisting comorbidities and important outcomes including use of KRT (dialysis or transplant), episodes of cancer, hospitalizations, and death. We will use these data to better understand the apparent gap between high community prevalence of CKD and low use of KRT.

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Conflicts of Interest

MJ is a member of the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) Executive Committee.

Multimedia Appendix 1
Variables received from pathology services.
[DOCX File , 13 KB - resprot_v9i9e20160_app1.docx]

Multimedia Appendix 2

ICD-10AM codes used to identify the cause of CKD.
[DOCX File , 13 KB - resprot_v9i9e20160_app2.docx]

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Abbreviations

ANZDATA: Australia and New Zealand Dialysis and Transplant Registry
CKD: chronic kidney disease
DEATH: Births, Deaths and Marriages Tasmania Fact of Death
DSPL: Diagnostic Services Pty Ltd (Hobart, Launceston, and North West Pathology)
eGFR: estimated glomerular filtration rate
ESKD: end-stage kidney disease
PPID: project person identifier
RHH: Royal Hobart Hospital

RHHPATH: Royal Hobart Hospital Pathology
SA2: Statistical Areas Level 2
SCr: Serum Creatinine
TCR: Tasmanian Cancer Register
TDLU: Tasmanian Data Linkage Unit

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Protocol

Reward Responsiveness, Optimism, and Social and Mental Functioning in Children Aged 6-7: Protocol of a Cross-Sectional Pilot Study

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Abstract

Background: There is evidence that reward responsiveness and optimism are associated with mental and social functioning in adolescence and adulthood, but it is unknown if this is also the case for young children. Part of the reason for this gap in the literature is that the instruments that are used to assess reward responsiveness and optimism in adolescents and adults are usually not suitable for young children.

Objective: Two behavioral tasks to assess reward learning, a questionnaire on reward responsiveness, and a questionnaire on optimism/pessimism will be tested on their feasibility and reliability in children aged 6-7. Depending on their feasibility and reliability, these instruments will also be used to investigate if reward responsiveness and optimism are associated with mental and social functioning in young children.

Methods: For this cross-sectional pilot study, we adapted a number of tasks and questionnaires to the needs of 6-7-year-old children, by simplification of items, oral rather than written assessment, and reducing the number of conditions and items. We will approach teachers and, with their help, aim to include 70 children aged 6-7 to assess the feasibility and reliability of the tasks and questionnaires. Feasibility measures that will be reported are the proportion of children completing the task/questionnaire, the proportion of children that were able to explain the instructions in their own words to the researcher, and the proportion of children that correctly answered the control questions. The reliability of the scales will be assessed by computing Cronbach α and item-total score correlations and the reliability of the tasks by correlations between different consecutive blocks of trials. Ethics approval was obtained from the Ethics Committee of the Department of Pedagogy and Educational Sciences.

Results: Data collection was originally planned in March and April 2020, but has been postponed due to Corona virus regulations. We expect to collect the data in the first half of 2021. The findings will be disseminated in preprints and peer-reviewed publications.

Conclusions: The development of feasible and reliable instruments for assessing reward responsiveness and optimism in young children is expected to benefit future research on underlying mechanisms of mental and social functioning in young children. If the instruments assessed in this study are usable with young children, it would be particularly interesting to include them in cohort studies because this would enable investigating not only concurrent associations, but also prospective associations between reward responsiveness and optimism early in life and mental and social functioning later in life. If, as we hypothesize, reward responsiveness and optimism are not only associated with (prospective) mental and social functioning in adults and adolescents but also in young children, this could provide a way of identifying vulnerable children already at an early stage.

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KEYWORDS

optimism; reward responsiveness; risk-taking; children; mental health; social relations

Introduction

Background

Research suggests that reward responsiveness and optimism are important for mental and social functioning in adults and adolescents [1-8]. Rewards play an important role in shaping our behavior in everyday life [9,10]. Rewards can be very diverse, for instance, monetary (eg, winning the lottery), winning a game, eating one's favorite meal, and social rewards (eg, being liked or receiving a compliment from a friend). People in general adapt their behavior in the presence or prospect of a reward, with the aim of maximizing the reward or increasing the chance of future rewards. That is, individuals learn from the conditions in which they receive rewards and adapt their behavior accordingly [11,12]. For example, if a certain strategy results in gaining points in a game, being liked by others, or receiving social praise, individuals will start using this strategy more often. This is a specific type of reward responsiveness, commonly referred to as *reward learning*. Although people generally respond strongly to rewards, individual differences can be observed with respect to the strength of the response. These differences can be important as there is ample evidence that low reward responsiveness is associated with current depression [1,2,13] and prospectively predicts depression [14-17]. Very high reward responsiveness is associated with other types of mental health problems, for example, addiction and criminal behavior [3,18]. There is also some evidence suggesting that reward responsiveness is associated with social functioning [17,19], that is, individuals with higher reward responsiveness show higher levels of sociability and emotional intelligence [19], and report higher friendship quality [17].

Not only reward responsiveness, but also optimism is important for mental and social functioning in adults and adolescents [4,20,21]. Optimism refers to the general belief that things will go well and that the future will turn out good rather than bad [5]. Optimists, when confronted with a setback, believe that this is not indicative of a personal weakness and are motivated to overcome the problem. Pessimists, by contrast, are more likely to have negative expectations about themselves and the people around them and are more likely to give up when faced with challenges. Compared to pessimists, optimists report higher levels of subjective well-being, better mental health, and are more liked by other people [6,22]. A more optimistic attitude toward life is, for example, associated with lower levels of depressive symptoms [6,21] and optimists are more socially accepted than those who show a less optimistic view on life [7,23]. More optimistic college freshmen experience more social support and report larger friendship networks [8]. However, unrealistic optimism has been found to be related to harmful risk-taking behavior [24].

There is evidence that reward responsiveness and optimism are associated with mental and social functioning in adolescence and adulthood, but it is unknown if this is also the case for young children. Part of the reason for this gap in the literature is that the assessment methods that are used for adolescents and adults are usually not suitable for young children. Another gap in the literature is the lack of knowledge about the relation between reward responsiveness and optimism. It seems plausible that high reward responsiveness extends to expectations about the future in that positive rather than negative information may primarily be used to form future expectations, which is characteristic of an optimistic view on life. Optimists tend to update their beliefs less based on negative experiences or information that is more negative than expected and update their beliefs more based on rewarding experiences or positive information [24,25]. Optimism may also lead to higher attention to rewards and lower attention to the negative aspects of life, even in stressful or difficult situations. However, to our best knowledge, associations between reward responsiveness and optimism have not been investigated directly, let alone in young children.

This Study

For this pilot study, we adapted a number of tasks and questionnaires to the needs of 6-7-year-old children, by reformulating questionnaire items, using oral rather than written assessment, and reducing the number of experimental conditions and questionnaire items. The adapted instruments will be piloted for feasibility, and will be used to investigate if reward responsiveness and optimism are associated with mental and social functioning already in young children. Associations between reward responsiveness and optimism will also be investigated. Importantly, if the new instruments work for young children, this could benefit many different types of future studies. It would be particularly interesting to include the instruments in cohort studies to facilitate investigating prospective associations. This would mean that, in time, we would be able to investigate whether reward responsiveness and optimism at age 6-7 prospectively predict mental and social functioning later in life. This information may ultimately inform preventive programs aimed at modifying reward responsiveness and optimism in early to middle childhood.

Research Questions

1. Do 6-7-year-old children understand the tasks and questionnaires and is the length of the tasks and questionnaires feasible for this young age group?

2. What is the reliability (ie, internal consistency) of the instruments?

3. Are individual differences in aspects of reward learning during the reward tasks associated with each other and with self-report measures of reward responsiveness and optimism in 6-7-year-old children? Reward learning outcomes are, for example, how fast children learn from the conditions in which they receive a reward and the extent to which they are willing to take risks to earn a reward.

4. Are individual differences in reward learning, reward responsiveness, and optimism associated with mental

functioning (teacher report) and social functioning (teacher and classmate reports) in 6-7-year-old children?

Methods

Sample and Procedure

We aim to include 70 children aged 6-7. A linear regression power analysis in G*Power 3.1 [26] showed that, with power set to 0.80 and α to .05, a minimum of 55 participants is required to find a moderate effect. A similar number of participants is required for a moderate correlation. An additional 15 participants will be recruited to compensate for possible drop out. Because of the explorative nature of this pilot study, we will not correct for multiple testing.

Complete school classes will be recruited (group 3 in the Dutch school system) via the teachers. Depending on the size of the classes and the number of parents willing to give consent for their children to participate in the study, we expect to include 4-7 school classes. Teachers will be approached by telephone, email, and social media. They will receive an information letter and a consent form. After a teacher has signed the consent form, the parents of the children in the class will be contacted. They will also receive an information letter and consent form. Only when the teacher and parents of a child give consent, the child will be included in the study. The child will be asked to give informed consent orally on the day of the assessment and will be assured that he/she can stop at any time during the assessment. Ethics approval was obtained from the Ethics Committee of the Department of Pedagogy and Educational Sciences of the University of Groningen (ref. 04032020).

Child assessment consists of 2 computer tasks and 3 short questionnaires (18 items in total). Children will be assessed individually in a separate room by a researcher who reads all instructions and items to the child, checks if the child understands them, and remains present during the entire assessment. After the final task, the researcher will ask the child what he or she liked and disliked about the tasks and if everything was clear. Additionally, for children who disclosed bullying, the researcher will ask if the child already talked about this with a parent, teacher, or other adult. If not, the child will be encouraged to do so and the researcher will offer to help with this. The estimated total duration of the child assessment is 30-40 minutes. Children will receive 3 stickers and a small present.

Teachers will receive a weblink to answer questions about the mental (8 items) and social functioning (9 items) of the participating children in their classroom, with an expected duration of 5-10 minutes per child. Teachers will receive a gift card of €40 (US $47) for participating in the study to purchase something for the class. Teachers will be debriefed individually by a researcher after all child assessments and online questionnaires are completed. Teachers of classes in which bullying was disclosed will be encouraged to discuss bullying in the classroom or with children individually, if they have not done so already. For privacy reasons, no information about experiences of specific children will be shared with teachers.

The tasks, questionnaires, and feasibility assessments will be described in detail per task in the “Measures” section.

Data will be stored on institutional network drives with security firewalls and access to the data will be limited to the study team. Data will be kept deidentified and a password-protected file with identifiers will be stored separately from the data. Raw data will not be shared publicly for reasons of privacy (ie, this would enable coupling children with certain unique task scores to teacher reports), but researchers interested in the data can submit a research proposal to the first author (CV) of this study protocol.

Measures

Reward Learning Tasks

Two tasks will be used to assess reward learning. Because it is possible that experience with one of the tasks can influence performance on the next task, half of the children in each class will start with one task and the other half with the other task. The second task will not be assessed directly after the first one, but only after a block of questions. Each child will be assessed individually by a researcher, who will score whether the child is able to explain the instructions in his/her own words to the researcher, and whether the child correctly answers the control questions asked by the researcher.

Task 1: Probability Learning Task: Finding Gold Coins (PL Gold Coin Task)

To assess reward learning, a computer task that has the appearance of a computer game will be used. The child is instructed to search for gold coins that have been hidden by an elf under 1 out of 6 rocks. Children are instructed to click with the mouse on the rock under which they think the gold coin is hidden. After choosing a rock, the child is shown if the coin is hidden there, and, if not, is shown the correct location of the coin. Every time the elf appears the child can search for a new gold coin, 120 times in total. Unknown to the child, the gold coins will be hidden under the same rock in 75% (90/120) of the cases, there are 2 rocks under which the coin is hidden in 10% (12/120) of the case, 1 rock under which the coin is hidden in 5% (6/120) of the cases, and 1 rock under which the coin is never hidden. The task assesses to what extent children adapt their search strategy to the most frequent location of the coin.

The task was originally developed by Plate and colleagues [27], who gave permission for its use and adaptation. The original task consisted of 8 rocks, 200 trials, and the largest proportion of gold coins under the same rock was 70%. The number of trials was too high for 25% of the children between ages 4 and 11 and for these children the data could not be used [27]. Therefore, we shortened the task to 120 trials, decreased the number of rocks from 8 to 6, and increased the largest proportion of gold coins under the same rock from 70% to 75%. We expect that these changes will ensure that children learn faster from the rewards than in the original task and that our shorter version of the task is still sufficient to assess individual differences in reward learning. A final adaptation to the original task is that the location of the rock with the largest proportion of gold coins will be varied among children. In the original task, this rock was always in the same location, somewhere in the middle, and

we want to prevent that choosing the middle rock more often than the more peripheral rocks is unjustly interpreted as a learning effect when it is actually a preference for central locations that is unrelated to reward learning. All of the changes we made to the original task were discussed with the researcher who developed the task.

The task is programmed in E-Prime 2 and will be assessed on a laptop. After 60 trials, the child is given a short break. The estimated total duration of the task, including instruction and break, is 12 minutes. After the instruction and before the actual task starts, the researcher checks whether the child understands the task by asking the child to explain the task to the researcher. If this is too difficult, the researcher asks the following more specific questions: *How do you search for gold coins?,What do you see on the screen if you have found a gold coin under a rock?*, and *What do you see on the screen if you picked the wrong rock?*

At the start of the task, the children are told that they get to choose a present from 1 of 3 boxes after completing the task. They are told they can choose a present from box 1 if they find a small number of coins, a somewhat larger present from box 2 if they find more coins, and a large present from box 3 if they find a large number of coins. It is part of the task that the children believe that the amount of gold coins they find determines the size of the present they receive. Unknown to the children, at the end of the task all of them will be told that they did a good job and can choose a present from box 3.

Task 2: The Balloon Emotional Learning Task (BELT)

In this task, a small colored balloon appears on the computer screen. The children are instructed that they can pump up the balloon by pressing the space bar. The more often they press the space bar, the more the balloon inflates. The larger they pump up the balloon, the more points the child earns, but no points are earned if the balloon pops. The child is told that some balloons are stronger than others and can be pumped up further before they pop. After each successful pump, the child needs to choose between pumping up the balloon further and pressing enter to cash the points earned for that specific balloon. If the balloon pops before the points are cashed, the child loses the points for that specific balloon. The tests consist of 45 balloons in total. Unknown to the children, the 3 different colors of the balloons represent their strength: the orange balloon always pops after 7 pumps, the pink balloon always pops after 19 pumps, and the blue balloon has a variable strength, popping after 7, 13, or 19 pumps. The task assesses how much risk the child is willing to take to obtain a larger reward and the extent to which the child learns from feedback about the circumstances (here, color of the balloon) under which risk taking results in reward and the circumstances under which it does not [28].

This task was developed by Humphreys and colleagues [28] and was used in children as young as 3 years of age. The original task consists of 29 balloons (trials), but the researchers themselves suggested that it would be better to use a longer task in future research [28]. We received permission to use the task and increased the number of trials from 29 to 45.

The task is programmed in E-Prime 2 and will be assessed on a laptop. Stickers will be used to make it easier for young children to remember the keys they need to use. That is, on the space bar, they will see a sticker of a balloon and on the enter key a picture of a prize meter, similar to the one they see on the screen. The estimated total duration of the task, including instruction, is 5 minutes. After the instruction and before the actual task starts, the researcher checks whether the child understands the task by asking the child to explain the task to the researcher. If this is too difficult, the researcher asks the following more specific questions: *How do you pump up a balloon?* or *What do you do if you want to stop pumping and save the points you've earned?*

To motivate the children to do their best, they are told that if they gain enough points they can choose 2 stickers at the end of the task. Unknown to the children, at the end of the task all of them will be told that they did a good job and can choose 2 stickers.

Child Questionnaire Measures

Similar to the tasks, each child will be assessed individually. A researcher will ask questions about the child's emotional responses to rewards, optimism/pessimism, and social experiences in the classroom. All instructions and questions will be read to the child and the researcher will enter the answers in Qualtrics (Qualtrics Inc.).

Pleasure Scale to Assess Emotional Responses to Rewards

To assess children's emotional responses to rewards, an adapted and shortened version of the Children's Pleasure Scale by Kazdin [29] will be used. We assess how happy a child feels if situations occur that are commonly perceived as pleasurable (eg, receiving a present, or a compliment). Children will be asked to rate each situation on a 3-point Likert scale and indicate if the situation would make them (1) very happy, (2) happy, or (3) it would not matter. A large card depicting 3 smileys (from very happy to neutral) paired with the 3 response options will be placed in front of the child and the child can either answer by talking or by pointing to one of the smileys. Before beginning the actual interview, the researcher checks if the child understands the response options by presenting the 3 response options to the child orally, in a different order than in the original explanation, and asking the child to point at the picture belonging to the specific response. If the child makes a mistake for one of the response options, all 3 are repeated until the child shows the correct response for all options. The child is also asked to respond to an example item (ie, *You get to eat a piece of candy you like*).

The original questionnaire has been used with 6-year-old children [29], but was not validated specifically for a young age group. Some questions seem rather complicated or not applicable to our young age group (ie, *You accidentally overhear your teacher bragging to the principal about what a terrific student you are*). With 39 items, the original questionnaire is also very long. Therefore, we simplified and shortened the original questionnaire and translated it into Dutch. In detail, our research team, including a former primary school teacher (AB) who has experience with our specific age group, selected 10 items based

on high item-total score correlations [29], relevance for our age group, and low level of difficulty. These items were translated, simplified (if necessary), and tested in a pilot. Five parents trialed the revised items with their 6-7-year-old children and reported that all of the children were able to answer the questions and indicated that the answers matched with what they would have expected their child to answer. Finally, we selected the 8 most relevant items with the least overlap, while retaining all 3 pleasure domains from the original questionnaire, that is, the domains of physical pleasure (ie, eating a favorite meal), social pleasure (ie, being told what a good friend you are), and other types of pleasure (ie, winning a game). See Multimedia Appendix 1 for the original items and the (translated) reformulated items.

Optimism/Pessimism

Optimism/pessimism will be assessed with an adapted and shortened version of the Youth Life Orientation Test (YLOT) [30,31]. Children are presented with different statements and are asked how often they think this: never, sometimes, often, or all the time. Following the procedure of Bamford and Lagattuta [31], a large card depicting 4 boxes ranging from empty to full, paired with the 4 response options, will be placed in front of the child. The child can answer by either talking or pointing to one of the boxes. Before beginning the actual interview, the researcher checks if the child understands all response options. The child is also asked to respond to 2 example items (ie, *I think fries are tasty* and *I like eating worms*).

The original questionnaire has been validated only among children aged 8 and older [30], consists of several questions about the future that are likely too difficult for 6-7-year olds, and was long (19 items). Based on a version adapted for and used with 6-year olds [31], but which still contained several difficult items (ie, *I'm always hopeful about my future*), we created a further simplified and shortened Dutch version. We followed a similar procedure as for the Children's Pleasure Scale. We first selected 8 items based on high item-total score correlations [30], relevance for the targeted age group and low level of difficulty. These items were translated and further simplified if necessary. Five parents trialed these questions with their 6-7-year-old children. Four of them reported back to us that their child had difficulties understanding the item *Usually, I don't think good things will happen to me*, therefore, this item was excluded. Parents reported that their children were able to answer the other questions and that the answers matched with what they would expect their child to answer. Finally, we selected the 6 most relevant items by dropping one more item because of overlap with another item. See Multimedia Appendix 1 for the original items and the (translated) reformulated items.

Social Experiences

To assess peer acceptance and rejection, children will be asked to nominate the children in their classroom they like to play with and the ones they do not like to play with. Peer aggression and peer victimization will also be assessed using peer nominations. Because of the wide range of reading abilities at ages 6 to 7, photographs are used to facilitate peer nomination in this young age group [32-34]. Children will be presented with a list including the names and photographs of the children in their classroom whose parents have consented, and are asked to either state the names or point to the pictures. The photographs will only be used during the assessment and will be destroyed directly afterward. For all peer nomination measures, proportion scores will be calculated (number of nominations/[number of participating children in the classroom – 1]); this is the gold standard for assessing acceptance and rejection [32].

The use of peer nominations with children sometimes raises the question of whether being assessed with these instruments may have negative consequences for the children. However, studies among children and their teachers suggest that children hardly show negative emotional responses after the use of peer nominations similar to the ones we will use, and also that children are not treated differently in the classroom afterward [35]. The youngest children in these studies were 8 years old, only slightly older than our sample, and we have no reasons to assume that results are different for our age group.

Teacher Questionnaires on Children's Mental and Social Functioning

Mental Functioning

Mental functioning of the children will be assessed with the Teacher's Checklist of Psychopathology (TCP). The TCP is a shortened version of the Teacher's Report Form [36] and was developed for the TRacking Adolescents' Individual Lives Survey (TRAILS) [37]. The TCP assesses 9 problem domains: Withdrawal, Somatic complaints, Anxious/depressed symptoms, Social problems, Thought problems, Attention problems, Activity/impulsivity, Aggressive behavior, and Delinquent behavior. The checklist includes descriptions of the corresponding problem behavior for each of these domains. Because we did not have a specific research interest in associations between reward responsiveness/optimism and somatic complaints, this domain (Somatic complaints) was excluded. For the domain Delinquent behavior, we removed parts of the description that were not age appropriate, for example, pertaining to skipping classes and using alcohol or drugs. (For the specific items, see Multimedia Appendix 2.)

Social Functioning

In addition to the classmates, teachers will also be asked about the children's social functioning. Whereas classmates can observe their peers' more subtle behaviors that may remain hidden for parents and teachers, teachers can provide an accurate general perspective on children's social functioning that is complementary to the perspective of classmates [35], and it has been advised to combine the 2 complementary perspectives [32]. Teachers will complete a questionnaire on peer aggression, peer victimization, and acceptance (9 items), as used in the Quebec Newborn Twin Study [38], for each of their students participating in the study (see Multimedia Appendix 2).

Statistical Analysis Plan

The feasibility of the tasks and questionnaires for 6-7-year-old children will be determined by calculating for each task and questionnaire the number of children that completed it, the

number of children that were able to explain the instructions in their own words to the researcher, and the number of children that correctly answered the control questions of the researcher prior to the assessment. The reliability of the scales assessing emotional responses to reward and optimism/pessimism will be determined by calculating Cronbach α. Item-total score correlations will also be reported. The reliability of the tasks will be assessed by calculating correlations between different consecutive blocks. Split-half reliabilities will not be computed, because we expect children to learn during the tasks and, therefore, would not expect the first and second half of a task to be highly correlated.

Although we aim to investigate relations between reward responsiveness and optimism and mental and social functioning in 6-7-year-old children, it depends on the feasibility and reliability of the child questionnaires and tasks if statistical tests of these associations are meaningful. In any case, we will report descriptive statistics for all measures. For all scales, sum scores will be reported. The following task outcomes will be reported: the number of points earned during the Probability Learning (PL) Gold Coin Task and the Balloon Emotional Learning Task (BELT), and the number of pumps (general risk taking) [39] and explosions (uncontrolled risk taking) during the BELT [39]. All BELT outcomes will be reported separately for the 3 different conditions (ie, colors). For both tasks, these outcomes will be reported for the task in total, as well as separately for the different blocks.

Results

Data collection was originally planned in March and April 2020, but has been postponed due to Corona virus regulations. We expect to collect the data in the first half of 2021. Results will be disseminated in deidentified and aggregated form in one or more preprints and peer-reviewed publications. Main findings of this study will be shared on social media and teachers who participate in the study will receive a report with the main findings. Additionally, if the tasks and questionnaires are usable for young children, they will be considered for inclusion in the next wave of the large intergenerational cohort study TRAILS Next [40].

Discussion

We will investigate the feasibility and reliability of tasks and questionnaires assessing reward learning, reward responsiveness, and optimism specifically for 6-7-year-old children, an age group often assessed in longitudinal birth-cohort studies. Our findings could benefit many researchers interested in studying reward responsiveness and optimism in young children. If the instruments assessed in this study are usable with young children, it would be particularly interesting to include them in cohort studies because this would enable investigating prospective associations between reward responsiveness and optimism early in life and mental and social functioning later in life, and may, ultimately, provide a way of identifying vulnerable children already at an early stage. Because of the exploratory nature of this pilot study, we do not correct for multiple testing, thus any results we find about associations between the different measures are tentative, awaiting replication in a different sample.

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Authors' Contributions

Each author has contributed significantly to the study. CV designed the study and TK provided critical revisions; CV, AB, and MA adapted the tasks and questionnaires to be suitable for children aged 6-7 and wrote the submission for the ethical committee; CV drafted the manuscript for the protocol, and TK, AB, and MA provided critical revisions. AB and MA contributed equally to this study.

Conflicts of Interest

None declared

Multimedia Appendix 1
All child questionnaire items used in the present study, including the Dutch translations and original formulations.
[PDF File (Adobe PDF File), 176 KB - resprot_v9i9e18902_app1.pdf]

Multimedia Appendix 2
All teacher questionnaire items used in the present study, including the Dutch translations and original formulations.
[PDF File (Adobe PDF File), 177 KB - resprot_v9i9e18902_app2.pdf]

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Abbreviations

BELT: Balloon Emotional Learning Task
PL: probability learning
TCP: Teacher's Checklist of Psychopathology
TRAILS: TRacking Adolescents' Individual Lives Survey
YLOT: Youth Life Orientation Test

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Protocol

Country-Level Assessment of Missed Opportunities for Vaccination in South Africa: Protocol for Multilevel Analysis

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Abstract

Background: Vaccination is one of the greatest public health interventions of all time. Vaccination coverage in South Africa has shown a steady improvement in reaching the national target. However, while there is progress nationally, there are districts within the country that are below the set target for vaccination coverage. One of the main drivers of suboptimal vaccination coverage is thought to be missed opportunities for vaccination.

Objective: This study aims to understand the magnitude and determinants of missed opportunities for vaccination in South Africa.

Methods: The 2016 South African Demographic and Health Survey will be used to conduct multilevel regression analyses to determine individual and contextual factors associated with missed opportunities for vaccination in South Africa. The perspectives of parents attending health care facilities in South Africa will be explored through exit interviews and focus group discussions. Similarly, perspectives of the health care providers will be sought to understand enablers and barriers to vaccination coverage at the facility level. Insights to such factors will aid in designing tailor-made interventions to improve vaccination coverage in South Africa.

Results: Ethical review submission is planned for October 2020. Data collection is expected to be underway in January 2021.

Conclusions: The extent of missed opportunities in South Africa coupled with the associated factors presents an opportunity for efforts to increase uptake in districts where vaccination coverage is below the national target. Population-level data such as those from the 2016 South African Demographic Health Survey will provide an idea of the magnitude of missed opportunities for vaccination in South Africa at the national and subnational levels. The findings of the study will inform national and subnational policy implementation on vaccinations and help to find context-specific interventions to improve vaccination coverage.

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KEYWORDS

South Africa; vaccination coverage; missed opportunities for vaccination; implementation science

Introduction

Background

Vaccinations currently save between 2 and 3 million children every year [1]. However, vaccines can only prevent childhood diseases if they reach the intended target populations [2]. In low- and middle-income countries, the benefits of vaccinations, which can be direct and indirect, are not being maximized for children, as routine immunization remains suboptimal [2]. Immunization coverage (with the third dose of diphtheria-tetanus-pertussis–containing vaccine; DTP3) had reached 90% by 2018 in 129 countries, the majority of which were high-income countries [3]. According to the World Health Organization (WHO), the 10 countries with the most unvaccinated children are Angola, Brazil, the Democratic Republic of the Congo, Ethiopia, India, Indonesia, Nigeria, Pakistan, the Philippines, and Viet Nam [3]. Immunization coverage is one of the key measures for assessing the performance of national immunization programs [4]. DTP3 is commonly used as a surrogate indicator for immunization [5]. Low- and middle-income countries are dependent on the Expanded Program on Immunization framework to ensure that all children receive their recommended vaccinations [6]. The Expanded Program on Immunization is supported by local health ministries to provide vaccinations to infants at no cost [4].

However, there are challenges related to accessing the Expanded Program on Immunization. These include accessing far-to-reach health care facilities, vaccine stock-outs in the facilities, and more importantly, missed opportunities for vaccination and vaccination hesitancy [7,8]. In addition to the challenges associated with the Expanded Program on Immunization, another important issue that affects vaccination coverage is poor data collection and reporting. Vaccination coverage data quality was highlighted in 2012 pointing to multiple issues surrounding data collection [9,10], compilation, and transfer in generating immunization data. Countries need to collect and report high-quality vaccination data to enable assessment of immunization performance. In turn, delivery of the vaccines to populations in need can be improve [6].

In South Africa, there has been substantial progress in immunization coverage, access to free health care, and prevention of malnutrition and mother-to-child transmission of HIV. However, the current levels of under-5 mortality in the South Africa are still very high indicating that the United Nation Sustainable Development Goals' target of less than 25 deaths per 1000 live births by 2030 may not be reached [11]. The top causes of under-5 mortality are neonatal conditions, diarrhea, pneumonia, and HIV-related infections [12]. Multiple efforts are being made to improve immunization coverage; there is a need for the improvement of health service delivery vis-a-vis establishing synergy between health programs to reduce missed opportunities for vaccination [10].

Missed opportunities for vaccination refer to any contact with health services by persons who are eligible for vaccination (eg, unvaccinated or partially vaccinated and free of contraindications to vaccination), which does not result in them receiving one or more of the vaccinations for which they are eligible [7]. Missed opportunities for vaccination occur in two major settings: (1) during visits for vaccination and other preventive services and (2) during visits for curative services. In both settings, eliminating missed opportunities will increase the overall immunization coverage in the population and thus prevent vaccine-preventable diseases.

Recommended strategies for reducing missed opportunities for vaccination emphasize the usefulness of periodic monitoring to evaluate the quality of vaccination program performance at the health service level as well as evaluating progress toward reducing missed opportunities [13].

The Expanded Program on Immunization is one of the most successful and cost-effective public health initiatives to reduce infant morbidity and mortality from vaccine-preventable diseases. The benefits of immunization are so immense that in 2011, the World Health Assembly put forth a resolution to declare a Decade of Vaccines (2011-2020) [4]. Furthermore, target 3.8 of the Sustainable Development Goals emphasizes the importance of immunization and, as such, calls for “access to safe, effective, quality and affordable medicines and vaccines for all” by 2030 [14]. Improved coverage of early childhood immunization is essential to achieving Sustainable Development Goals goal 3.8. Gavi, the Vaccine Alliance is calling for a universally applicable vaccine indicator to “reach and sustain 90% national coverage and 80% in every district with all vaccines in national programs” to be one of the measures of Sustainable Development Goal 3.8 [15].

Additionally, further research is needed to assess various factors attributed to missed opportunities in different districts across the country. The proposed study will provide novel insights on the magnitude and determinants of missed opportunities for vaccination to enable tailor-made strategies for addressing various factors unique to different districts, thus filling the key knowledge gaps, which is important for achieving vaccination goals in South Africa. Given the pragmatic nature of the project, its involvement of key national vaccination stakeholders and provincial and district stakeholders will generate knowledge that has the potential to inform policy decisions at the national level and which can easily be implemented at provincial and district levels.

Aims and Objectives

The objectives of the study are as follows: (1) to examine the influence of individual-, neighborhood- and province-level socioeconomic factors on missed opportunities for vaccination in South Africa; (2) to explore reasons for missed opportunities for vaccination from the perspectives of caregivers of children aged 0-23 months attending primary health care facilities in Western and Eastern Cape provinces of South Africa; (3) to explore reasons for missed opportunities for vaccination from the perspectives of health care providers in primary health care facilities in Western and Eastern Cape provinces of South Africa.

Methods

Preliminary Identification of Factors

We will use the 2016 South African Demographic and Health Survey (SADHS). This will be a cross-sectional study. Briefly, the SADHS is a nationally representative household survey conducted in South Africa which uses a multistage, stratified sampling design with households as the sampling unit. Within each sample household, women and men meeting the eligibility criteria are interviewed. The survey findings represent the full target population because the samples are not self-weighting, and therefore, account for unequal selection probabilities as well as nonresponses [16]. SADHS is composed of a household questionnaire, a women's questionnaire, and in most countries, a men's questionnaire. We will use the WHO's definition of missed opportunities for vaccination as the outcome variable, defined as a binary variable that takes the value of 1 if the child 12-23 months had any contact with health services but remained unvaccinated to any vaccination dose for which the child is eligible. Contact with health services will be defined using the following 6 variables: skilled birth attendance, baby postnatal check within 2 months, received vitamin A dose in first 2 months after delivery, had health care and medical treatment of diarrhea, fever, or cough. We will limit the analysis to one child per woman to minimize the overrepresentation of women with more than one child in the age category. Individual-level factors will be included in the models: child's age, sex of the child (male versus female), high birth order (>4 birth order), child's birth weight, number of children under the age of 5 years in the household, maternal age completed years (15 to 24, 25 to 34, 35 or older), employment status (working or not working), maternal education (no education, primary, or secondary or higher), and media access (radio, television, internet, or newspaper). SADHS does not collect direct information on household income and expenditures. We will use the SADHS wealth index as a proxy indicator for socioeconomic status. The methods used in calculating the SADHS wealth index have been described elsewhere [17,18].

An index of economic status for each household will be constructed using principal components analysis based on the following household variables: number of rooms per house and ownership of a car, motorcycle, bicycle, fridge, television, and telephone, as well as any kind of heating device. From these criteria, the SADHS wealth index quintiles (poorest, poorer, middle, richer, and richest) will be calculated and used in the subsequent modeling. Clustering within the same geographical living environment will be described as a neighborhood. Neighborhoods will be based on sharing a common primary sample unit within the SADHS data [19,20]. We will consider neighborhood socioeconomic disadvantage for the community-level variable in this study. Neighborhood socioeconomic disadvantage will be operationalized with a principal component comprised of the proportion of respondents with no education (illiterate), unemployed, rural resident, and living below the poverty level (asset index below 20% poorest quintile). A standardized score with mean 0 and standard deviation 1 will be generated from this index; with higher scores indicative of lower socioeconomic position. We will divide the resultant scores into 5 quintiles to allow for nonlinear effects and provide results that are more readily interpretable in the policy arena.

Participant Sampling

We purposively selected the Western Cape and Eastern Cape provinces for the study to represent the urban and rural settings. The minimum sample required is estimated at 620 in the two provinces which will include both the parents and health care providers This sample size will be used for quantitative surveys and focus group discussion data collection. While the sample size has been estimated, this type of analysis allows reiteration to ensure that saturation is obtained. The estimation is based on the following assumptions: a prevalence of missed opportunities for vaccination of 32.2%, from a previous study [21]; an acceptable margin of error of 5%; nonresponse rate of 20%; and a design effect of 1.5 [21-23]. Design effect will be considered to account for clustering since respondents are embedded within specific health facilities [22-24]. For feasibility and logistical reasons, 10 primary health care facilities in each of the 2 districts—OR Tambo District in the Eastern Cape Province and Cape Town Metropolitan Municipality in Western Cape Province—will be randomly selected by cluster sampling technique. Each selected primary health care facility will be considered as a cluster. From each selected primary health care facility, all eligible and consenting caregivers with a child aged 0-23 months will be included.

For the focus group discussions, a purposively selected group of parents of children aged 0-23 months attending the selected facilities will be sampled from the participating primary health care facilities, based on findings from the quantitative analyses to incorporate diversity in terms of socioeconomic status, race, and class. Each group will comprise of 6 to 10 mothers. Selected parents (or caregivers) will be homogenous in terms of place of residence which allows the views by class, socioeconomic status, and level of education. In each province, at least 3 focus group discussions will be conducted. If necessary, additional sessions will be held until data saturation is reached.

For the in-depth interviews, we will purposively select 10 health facility staff, including vaccinators, clinical staff, and facility managers. Participants will be selected by taking into consideration roles, gender, and geographic location.

Participant Recruitment

Before participant recruitment, all necessary approvals from the regulatory and provincial health departments will be obtained. Participants will be recruited in the selected primary health care clusters with the assistance of the health care workers in those facilities. We will recruit parents (or caregivers) bringing their children for vaccinations to take part in the exit interviews. All participants will be asked to consent to participating by signing an informed consent form. Once participants enrolled in the study complete their exit interviews, appointments for the focus group discussions will be organized.

Previous research in South Africa [25,26] has identified that the vast majority of missed opportunities for vaccinations are caused by health facility obstacles, and thus health care workers will also provide informed consent to participate in the study

to understand service provider-perspective on missed opportunities for vaccination and collaboratively find interventions that are most suited for those settings.

Data Collection

Exit Interviews

Face-to-face interviews will be conducted for both parents (or caregivers) and health care providers. For parents, quantitative data will be collected through face-to-face exit interviews using an interviewer-administered structured questionnaire. This questionnaire is an adaptation of a WHO tool for assessing missed opportunities for vaccination in health care settings [27]. The exit interview questionnaire that will be used in this study has 6 sections: (1) data on the child; (2) data on the child's caregiver (or mother); (3) use of vaccination card and information on vaccination administered; (4) today's vaccination; (5) quality of the vaccination service; (6) reasons for getting vaccinated. Exit interviews will be conducted by trained (male and female) staff, who are fluent in both English and the South African Language most spoken in the study area. They will administer the structured questionnaire using mobile tablets. Pilot testing of the questionnaire will be conducted in a separate local area to ensure clarity and suitability of the questions. Data will be collected using REDCap (Vanderbilt University) mobile app on mobile tablets. Data quality assurance will be done using key/value pairs. Data collected will be stored on a secured database. After quantitative data collection, the data file will then be exported from REDCap to STATA (version 14.1; StataCorp LLC) for analysis. For the qualitative data, we will use NVivo (version 1.0; QSR International) to assist with data management and analysis. All personal identifiers will be removed from the interview and discussion transcripts before analysis. All recordings will be deleted upon completion of the study.

In-depth Interviews

Semistructured interviews will allow for in-depth exploration of the contextual factors and mechanisms of missed opportunities for vaccination from the experiences and perspectives of health workers and facility managers in the selected primary health care facilities.

All sessions will be conducted in private rooms within the selected health facilities, at a convenient time for the participants. The interview process will be open-ended and flexible, allowing participants the freedom to develop and deeply express their responses.

Focus Group Discussions

A qualitative research design will be used to explore the reasons for missed opportunities for vaccination from the perspectives of parents (or caregivers) [28]. Focus group discussion will be conducted face-to-face in a private room within the health facilities, at a convenient time for the participants. Discussions will last approximately one hour each. Each participant will be allowed to contribute during discussion and will maintain a circular sitting arrangement. A semistructured question guide will be used during the discussion. Participants will be asked about their experiences, and perception regarding vaccination, vaccination services and missed opportunities for vaccination. This question guide will be piloted in a primary health facility in South Africa to ensure clarity and suitability of questions.

Data Management and Analysis

Quantitative Data Management and Analysis

For SADHS data, descriptive analysis will be used to describe the distribution of respondents by key variables. Multivariable logistic multilevel regression models will be used to analyze the association between individual compositional and contextual factors associated with missed opportunities for vaccination. We will specify a 3-level model for binary response reporting missed opportunity for vaccination or not, for a child (at level 1), in a neighborhood (at level 2), living in a province (at level 3). Models will be constructed as (1) an empty or unconditional model without any explanatory variables, specified to decompose the amount of variance that exists between province and neighborhood levels; (2) containing only individual-level factors; (3) containing only neighborhood-level factors; (4) containing only province-level factors; and (5) simultaneously controlled for individual-, neighborhood- and province-level factors (full model).

For quantitative data from exit-interviews, missed opportunities for vaccination will be calculated using child's date of birth and date at which the last vaccination doses were administered. This will then be compared to the standard due date to determine if a missed opportunity has occurred. Children who are fully immunized for age will be categorized as *no missed opportunities for vaccination* while those who are not fully immunized for age will be categorized as *missed opportunities for vaccination*. Explanatory variables will be grouped into 3 levels as follows: (1) child-related factors (age of child, sex of the child, birth order); (2) caregiver-related factors (relationship with a child, marital status, level of education, occupation, mode of transport to the health facility, duration of transport to the health facility, exposure to media); and (3) health facility–related factors (refusal to offer vaccination, checking of vaccination card, charged fee for vaccination, charged fees for vaccination card, location characteristics, type of health facility, number of health workers, number of vaccinators). The distribution of explanatory variables (child, parent, and facility-related factors) by the outcome (missed opportunity for vaccination) will be calculated. We will specify a 2-level model for binary response reporting missed opportunity for vaccination or not with child and parent (or caregiver) as level 1, both nested within primary health care facilities (as level 2). Models will be constructed as (1) an empty (null) model with no explanatory variable; (2) containing only individual-level (child and caregiver) factors; (3) containing only facility-level factors; and (4) simultaneously controlled for child and caregiver-related and facility-level factors (full model).

The results of fixed effects (measures of association) will be reported as odds ratios with 95% credible intervals—95% CrIs. This Bayesian statistical inference approach provides probability distributions for measures of association, which can be summarized with 95% credible intervals, rather than 95% confidence intervals. A 95% credible interval can be interpreted

as a 95% probability that the parameter takes a value in the specified range.

The possible contextual effects will be measured by the intraclass correlation and median odds ratio [29,30]. We will measure the similarity between respondents in the same neighborhood and within the same province using intraclass correlation. The intraclass correlation represents the percentage of the total variance in the probability of missed opportunities for vaccination that is related to the neighborhood- and province-level (ie, measure of clustering of odds of missed opportunities for vaccination in the same neighborhood and province). The median odds ratio measures the second- or third-level (neighborhood or province) variance as odds ratios and estimates the probability of missed opportunities for vaccination that can be attributed to neighborhood and provincial context. A median odds ratio equal to one indicates no neighborhood or province variance. Conversely, the higher the median odds ratio, the more important the contextual effects are for understanding the probability of missed opportunities for vaccination. We will check for multicollinearity among explanatory variables by examining the variance inflation factor [31], all diagonal elements in the variance-covariance matrix for correlations between –1 and 1, and diagonal elements for any elements close to 0.

MLwinN software (version 3.0; University of Bristol) will be used for the analyses [32]. Parameters will be estimated using the Markov chain Monte Carlo procedure [32]. The Bayesian deviance information criterion will be used as a measure of how well the different models fitted the data. A lower value on deviance information criterion indicates a better fit of the model [33]. Scatter plots of performance, as a percentage, against the number of missed opportunities for vaccination children (the denominator for the percentage) will be generated. The mean provincial performance and exact binomial 3-sigma limits will be calculated for all possible values for the number of cases and used to create a funnel plot using the method described by Spiegelhalter [34,35]. If a province lies with the 99% CI, it has a crude missed opportunities for vaccination rate that is statistically consistent with the average rate (common-cause variation). If a country lies outside the 99% CI, then it has a crude missed opportunities for vaccination rate that is statistically different from the average rate (special-cause variation).

Qualitative Data Management and Analysis

Focus group discussions will be recorded using a portable audiorecorder and transcribed verbatim. Transcription will be done by a professional; however, each transcript will be checked for accuracy by the principal investigator. For the in-depth interviews, the template analysis approach will be used for coding and organizing data segments for analysis [36]. This method allows for flexible thematic analysis as the codebook can be adapted to the context of the study [37]. Two codebooks will be developed. The first codebook will specify factors identified from the discussion. For this codebook, the themes will be identified inductively [38]. In the second codebook, domains of the theoretical domains framework will be specified [39]. This is a validated framework with 14 domains that is useful for identifying barriers in implementation research [39]. The themes identified in the first codebook will be deductively adapted to domains of the theoretical domains' framework. The coder will identify causes of missed opportunities for vaccination from the interview transcripts, and then map each identified factor to a domain of theoretical domains framework. To avoid overlapping codes, only the most relevant code will be mapped to a particular domain. Coded data will be used for analysis. Analysis summaries for a combination of factors will be used to populate an analytic matrix. Illustrative quotations will be used in analytical summaries.

Integrative Analysis (Mixed Methods Approach)

We will conduct a mixed methods approach to integrate the quantitative data collected through the 2016 SADHS and structured questionnaires from exit interviews of caregivers, the qualitative data collected through the focus group discussions of parents (or caregivers) of children aged 0-23 month, and the qualitative data collected from the in-depth interviews of health care providers. Methodological integration considerations will be taken in the design, analysis, and reporting stages of the study. We will adopt the convergent design to better understand the complexity of missed opportunities for vaccination from the perspectives of caregivers and health care providers. The convergent design will compare both quantitative and qualitative data analyzed at the same time followed by an integrative analysis [40]. From the thematic analysis of the qualitative data, themes will be compared with the corresponding variable from questionnaires, and the results will be displayed as qualitative summaries and quotations for each domain-participant combination, thus allowing a full understanding of the complexity surrounding missed opportunities for vaccination from the health care service user [40,41].

Considerations

Ethical approval will be obtained from the South African Medical Research Council. We will also obtain permission from the appropriate authority of the South African Department of Health. The study process will comply with the requirements of the latest version of the Declaration of Helsinki (7th revision, 2013). Verbal and written information about the study will be provided to all participants taking part in interviews and focus group discussions. For the qualitative data, with permission of participants, all interviews and focus groups will be digitally recorded and subsequently transcribed verbatim. All digital recordings will be erased following transcription, and all identifying information will be removed from transcripts. Participant confidentiality and anonymity will thus be ensured. The consent form will make explicit the following aspects: the voluntary nature of participation, that there will be no negative consequences if they decide not to participate, that they will explicitly be asked for permission for the interview to be digitally recorded, and that this is also voluntary. Written consent will be obtained from all research participants before proceeding with interviews or focus groups.

Details from interviews and focus group discussions will be entered into a study-specific database on the day of collection (stakeholder group, participant ID, etc). Study data, including audio recordings, will be stored on password-protected

computers and shared with the study team only. All digital recordings on recorders will be destroyed following safe storage and transcription, and identifying information will be removed from all transcripts. Reports of the findings will not identify individual participants. Participant anonymity and confidentiality will thus be ensured.

No risks to participants or researchers are expected. All potential participants for interviews or focus groups are not considered to be vulnerable individuals or groups. However, participants may be uncomfortable expressing criticisms of vaccination programs. Where there is this potential, and where participants identify concerns, we will reassure participants of the steps that will be taken to ensure confidentiality. For participants in focus groups, we will remind participants at the outset that while the researchers undertake to maintain confidentiality, we cannot guarantee that other focus group participants will. At the start of the focus group, we will discuss the importance of everyone involved maintaining confidentiality after the focus group but will explain that there is an inherent risk of breaches of confidentiality in this method. We will ensure that participants are aware of this risk.

Results

Ethical review submission is planned for October 2020. Data collection is expected to be underway in January 2021.

Discussion

General

Not much is known about the burden and determinants of missed opportunities for vaccination in South Africa. Although a 2015 cross-sectional study conducted across selected health facilities in Cape Town found a low prevalence of 5% for missed opportunities for vaccination among children aged 0 to 5 years, the magnitude of the burden remains uncertain [42]. The study [42] found inadequate immunization training and knowledge among health care providers, as well as heavy workloads, as the main factors associated with missed opportunities to vaccinate children. In South Africa, the value that vaccinations deliver remains far below the substantial benefits that they can offer [43]. While there have been significant investments and efforts in ensuring universal access to immunization services in South Africa, it is evident that in some districts and many neighborhoods, there are eligible children who are missing out on this very critical health intervention [44,45]. How much of this gap is due to missed opportunities for vaccination remains uncertain. The mechanism and contextual factors associated with missed opportunities for vaccination in South Africa are less certain, and therefore, this study seeks to unpack these contextual factors in efforts to improve vaccination coverage in South Africa.

Our multilevel analytical approach considers the hierarchical structure of 2016 SADHS data and will enable us to simultaneously examine the effects of individual and contextual factors on missed opportunities for vaccination. Furthermore, we will use an innovative mixed methods approach to integrate quantitative and qualitative data from the SADHS, exit interviews, focus group discussions, and in-depth interviews, to better understand the complexity of missed opportunities for vaccination from multiple perspectives.

While there is currently limited evidence on the structural and contextual factors responsible for missed opportunities for vaccination in different contexts, research efforts in this area have increased in recent years. As a result, there has been an increasing body of evidence on the prevalence of missed opportunities for vaccination and associated factors over the last decade, including in African and other low- and middle-income countries contexts [46-51]. To date, however, there remain enormous gaps in what is known. Particularly, very little evidence exists on the burden and determinants of missed opportunities for vaccination in South Africa [42]. Much less certain is the evidence on the role and effectiveness of interventions for addressing missed opportunities for vaccination, with very little evidence on these in Africa, and none in South Africa [52].

Understanding the burden and mechanisms of missed opportunities for vaccination is important for policy and practice as it will provide valuable evidence to enable policymakers and facility managers to consider context-appropriate interventions for strengthening immunization programs. It will help inform institutions of context-appropriate and locally responsive immunization strategies and interventions to optimize immunization access and coverage. Therefore, this study will have local and national policy and practice implications in South Africa and Africa, in general. It will inform strategies for ensuring equitable and improved immunization coverage toward the attainment of the WHO Global Vaccine Action Plan targets, Universal Health Coverage agenda, and health-related UN Sustainable Development Goals.

Dissemination of Findings

The findings of the study will be shared with stakeholder groups, at consultation workshops, and on Cochrane South Africa websites. At the end of the study, a project report will be shared with all stakeholders who took part in interviews, focus groups, and consultation workshops. The findings will also be communicated through academic publications and conferences. Reporting of the qualitative data will adhere to COREQ [53] guidelines.

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Authors' Contributions

The study was initially conceived by CSW, and the methods for data collection were designed by OAU with contributions from SC and AAA for the aspects of qualitative research and implementation. DN wrote the first manuscript. DN, NJN, AAA, CN, TM, AML, SC, OAU, and CSW contributed to reviewing and shaping the direction of the protocol. All the authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

COREQ: Consolidated Criteria for Reporting Qualitative Research
DTP3: third dose of diphtheria-tetanus-pertussis–containing vaccine
HIV: human immunodeficiency virus
PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
SADHS: South African Demographic and Health Survey
WHO: World Health Organization

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Protocol

Evaluation of the Effectiveness of a Novel Brain-Computer Interface Neuromodulative Intervention to Relieve Neuropathic Pain Following Spinal Cord Injury: Protocol for a Single-Case Experimental Design With Multiple Baselines

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Abstract

Background: Neuropathic pain is a debilitating secondary condition for many individuals with spinal cord injury. Spinal cord injury neuropathic pain often is poorly responsive to existing pharmacological and nonpharmacological treatments. A growing body of evidence supports the potential for brain-computer interface systems to reduce spinal cord injury neuropathic pain via electroencephalographic neurofeedback. However, further studies are needed to provide more definitive evidence regarding the effectiveness of this intervention.

Objective: The primary objective of this study is to evaluate the effectiveness of a multiday course of a brain-computer interface neuromodulative intervention in a gaming environment to provide pain relief for individuals with neuropathic pain following spinal cord injury.

Methods: We have developed a novel brain-computer interface-based neuromodulative intervention for spinal cord injury neuropathic pain. Our brain-computer interface neuromodulative treatment includes an interactive gaming interface, and a neuromodulation protocol targeted to suppress theta (4-8 Hz) and high beta (20-30 Hz) frequency powers, and enhance alpha (9-12 Hz) power. We will use a single-case experimental design with multiple baselines to examine the effectiveness of our self-developed brain-computer interface neuromodulative intervention for the treatment of spinal cord injury neuropathic pain. We will recruit 3 participants with spinal cord injury neuropathic pain. Each participant will be randomly allocated to a different baseline phase (ie, 7, 10, or 14 days), which will then be followed by 20 sessions of a 30-minute brain-computer interface neuromodulative intervention over a 4-week period. The visual analog scale assessing average pain intensity will serve as the primary outcome measure. We will also assess pain interference as a secondary outcome domain. Generalization measures will assess quality of life, sleep quality, and anxiety and depressive symptoms, as well as resting-state electroencephalography and thalamic γ-aminobutyric acid concentration.

Results: This study was approved by the Human Research Committees of the University of New South Wales in July 2019 and the University of Technology Sydney in January 2020. We plan to begin the trial in October 2020 and expect to publish the results by the end of 2021.

Conclusions: This clinical trial using single-case experimental design methodology has been designed to evaluate the effectiveness of a novel brain-computer interface neuromodulative treatment for people with neuropathic pain after spinal cord injury. Single-case experimental designs are considered a viable alternative approach to randomized clinical trials to identify evidence-based practices in the field of technology-based health interventions when recruitment of large samples is not feasible.

Trial Registration: Australian New Zealand Clinical Trials Registry (ANZCTR) ACTRN12620000556943; https://bit.ly/2RY1jRx

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KEYWORDS

EEG neurofeedback; neuropathic pain; spinal cord injury; thalamus; serious games; brain-machine interface; brain-computer interface; single-case experimental design

Introduction

Background

Approximately 50% of individuals with spinal cord injury (SCI) report ongoing neuropathic pain at or below the level of injury [1-3]. Neuropathic pain is often accompanied by depression, anxiety, and poor sleep quality in this population [4,5], resulting in decreased health-related quality of life [6]. Despite the availability of analgesic medications and other pain therapies, no effective treatment has been found that benefits the majority of individuals with SCI, and most of the available treatments have significant negative side effects or risks of serious adverse events [7,8]. For example, the most powerful analgesics provide about a 50% reduction in pain intensity for only one-third of individuals with SCI [9], and they are associated with severe adverse effects such as toxicity [7]. While nonpharmacological interventions have minimal negative side effects [10-12], a Cochrane systematic review for chronic pain following SCI [8] found limited evidence of pain reduction across trials using repetitive transcranial magnetic stimulation, cranial electrotherapy stimulation, transcutaneous electrical nerve stimulation, acupuncture, hypnosis, or cognitive behavioral therapy. Hence, numerous people with SCI experience ongoing neuropathic pain on a daily basis with no access to effective treatment regimens.

The Critical Role of the Thalamus in Neuropathic Pain Following SCI

Although many brain regions are involved in the experience of neuropathic pain, Gustin and colleagues have identified the key role of the thalamus in the development and maintenance of neuropathic pain following SCI. They have found that neuropathic pain after SCI is associated with altered thalamic volume [13], neurochemistry [14], and blood flow [14]. Gustin and colleagues [14] suggested that a loss of cortically projecting ventral posterior thalamus neurons results in decreased excitatory input to the thalamic reticular nucleus. As a consequence of decreased thalamic reticular nucleus activity, the γ-aminobutyric acid (GABA) content of the thalamus is reduced. This reduction in thalamic reticular nucleus inhibitory output disrupts normal thalamocortical rhythms. It is postulated that this disruption of thalamocortical rhythms results in ongoing neuropathic pain following SCI [14,15].

The disruption in thalamocortical rhythms (thalamocortical dysrhythmia) can be detected by surface electroencephalography (EEG) [15,16]. EEG signals can be assessed as different frequency bands, such as theta (4-7 Hz), alpha (8-12 Hz), and beta (13-30 Hz). Thalamocortical dysrhythmia is characterized by a common resting-state EEG pattern of increased theta and low-frequency alpha rhythms [17,18]. The increased theta and low alpha frequency powers are further associated with an increase in beta frequency power [19]. For example, Sarnthein and colleagues [15] showed increased EEG activity in delta (2-3.5 Hz), theta (4-7.5 Hz), and beta (13-21 Hz) frequency powers in individuals with neuropathic pain compared with healthy study participants. Boord and colleagues [20], as well as Jensen and colleagues [16], showed similar results for individuals with SCI neuropathic pain having increased theta and decreased alpha frequency powers compared with individuals with SCI who had no pain and healthy study participants.

Changing Brain Rhythms Reduces Neuropathic Pain Following SCI

There is accumulating evidence that thalamocortical dysrhythmia can be self-regulated by neuromodulative interventions [21]. For example, brain-computer interface (BCI) systems have been used to reduce neuropathic pain after SCI via EEG neurofeedback [22,23]. In BCI-based neuromodulative (BCI-N) interventions, the electrical brain activity is monitored, processed, and provided back to participants in real time via visual or auditory feedback. Using this feedback, individuals can learn to regulate their brain activity in a way that reduces their pain.

Three single-arm trials have demonstrated that BCI-N interventions can reduce SCI neuropathic pain [22-24]. These studies used a BCI-N protocol, which consisted of suppressing theta and low-frequency alpha rhythms (4-8 Hz), and high-frequency beta rhythms (20-30 Hz), along with enhancing high-frequency alpha rhythms (9-12 Hz). Although these preliminary studies suggested that BCI-N can be effective in reducing SCI neuropathic pain, further studies are needed to

provide more definitive evidence regarding the effectiveness of BCI-N interventions for people with neuropathic pain following SCI.

Current BCI-N interventions for both SCI neuropathic pain [20,22,24] and chronic pain [25-27] have mostly relied on a single mode of virtual interaction, such as increasing or decreasing the height of a bar presented on a computer screen. However, preliminary evidence suggests that greater pain relief may be achieved from interactive, goal-directed engagement with a gaming environment, in comparison with a single virtual interaction format [28-31]. The increased analgesic effect may be due to the greater cortical involvement, which occurs during engagement with multiple scenarios in a goal-directed manner such as gaming [32]. Based on this evidence, we will use a self-developed BCI-N intervention that uses 3 virtual interactive scenarios in a goal-directed gaming environment to reduce SCI neuropathic pain.

Objectives

The primary objective is to evaluate the effectiveness of a multiday course of BCI-N intervention in a gaming environment to provide pain relief for individuals with SCI neuropathic pain. The secondary objective is to assess the intervention's effectiveness on participants' pain through pain interference. We will also determine whether the BCI-N intervention improves mood, sleep quality, quality of life, and well-being. Lastly, we will explore the neural mechanisms underlying the effect of a BCI-N intervention on SCI neuropathic pain. In particular, we will measure resting-state EEG and levels of thalamic GABA content pre- and postintervention.

Methods

Study Design

This study will be conducted based on a single-case experimental design (SCED) with multiple baselines across participants. The SCED is a powerful and effective method that is increasingly used in clinical trial designs [33,34] to evaluate preliminary effectiveness of an intervention [35-37]. Indeed, it has been argued that under the right circumstances, highly controlled SCEDs should be considered on par with traditional group-based randomized clinical trials [38]. An important strength of SCEDs with multiple baselines across participants is that it allows one to determine whether any change observed in the dependent variables occurs when, and only when, the intervention is directed at a particular participant [36]. As a result, the individualized findings of a highly controlled SCED trial can be accumulated to produce results equivalent to those found in randomized clinical trials but requires fewer participants for the same power [38,39]. Thus, the SCED approach is particularly useful when recruiting a large number of individuals into a clinical trial is not feasible.

The SCED method is based on assessing the dependent variables (in this case, pain intensity and pain interference) repeatedly for each of the participants across phases. The design of this study will be AB + follow-ups, where A refers to the baseline phase, B is the intervention phase, and both are followed by a follow-up phase. In addition, we will conduct a further follow-up phase 3 months after completion of the intervention. We will conduct and report the SCED study in accordance with the Single-Case Reporting Guideline in Behavioural Interventions (SCRIBE) 2016 Statement [40]. To meet the SCRIBE reporting standards, there must be at least three participants in a SCED with multiple baselines and more than five assessments of each dependent variable in each phase.

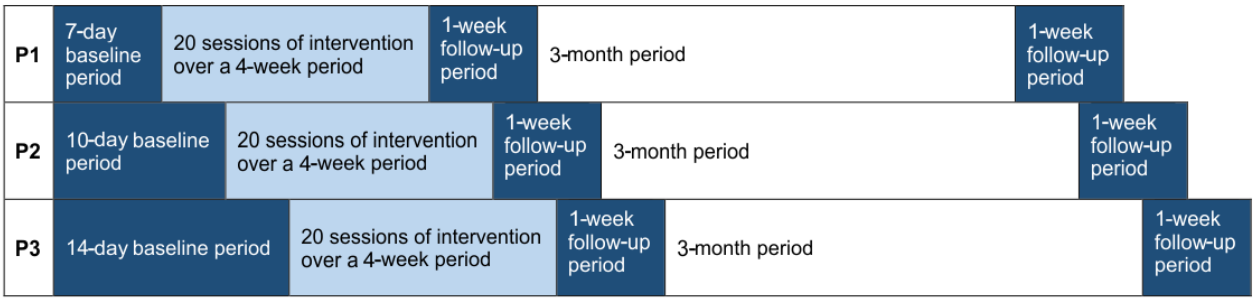
Participants

We will recruit 3 individuals with complete thoracic SCI (American Spinal Injury Association Impairment Scale A) for this study. Participants need to meet the following inclusion criteria: (1) aged 18 to 80 years, (2) having persistent neuropathic pain for 6 months or longer, (3) having an average pain intensity of 2 or more (out of 10) in the past week on a visual analog scale (VAS; with 0 cm reflecting no pain to 10 cm reflecting the maximum pain imaginable), (4) being medically stable, and (5) demonstrating an ability to use the VAS. With regard to the neuroimaging component of the study, we will exclude individuals who have metal objects inside their body (eg, stents, metal clips, implants, and shrapnel).

Procedure

We will randomly assign 3 participants to different baseline durations of the SCED using a simple randomization method [41]. Conventionally, a minimum of 3 baseline observation days are required to establish stability for the dependent variable [42]; however, more observations are preferred. In this study, we will obtain a stable baseline by using 7 days of observation. We will randomly assign each participant to 1 of 3 experimental conditions characterized by the length of the baseline phase. The first participant will have a 7-day baseline, the second participant will have a 10-day baseline, and the third participant will have a 14-day baseline. All participants will start the baseline phase on the same day. Each baseline phase will be followed by 20 days of a 30-minute BCI-N intervention over a 4-week period. Subsequently, there will be a 1-week follow-up for each participant to continue reporting the primary and secondary outcome measures in order to monitor possible changes in pain intensity and pain interference after completion of the intervention. In addition, we will conduct a further 1-week follow-up 3 months after completion of the intervention. Figure 1 summarizes the study procedure.

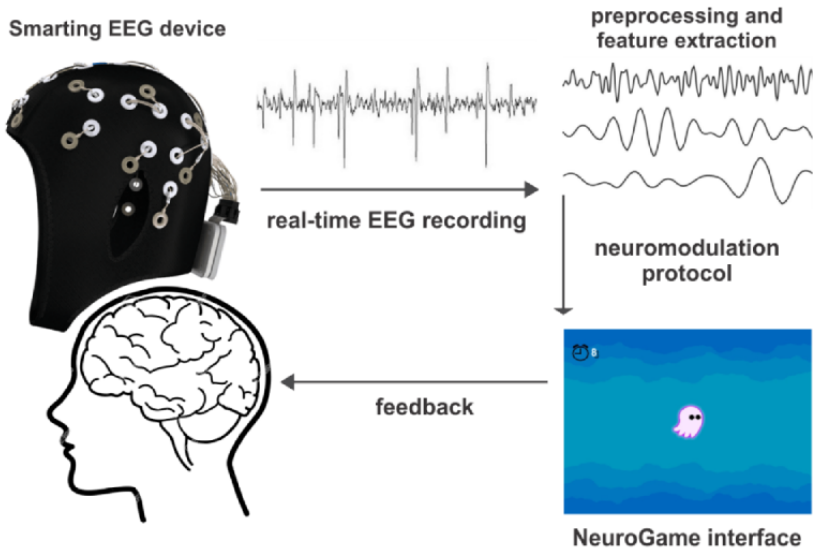
Figure 1. Study procedure. Each participant (P1-3) will be randomly allocated to 1 of 3 baseline periods. Each baseline phase will be followed by 20 days of a brain-computer interface (BCI)-based neuromodulative intervention over a 4-week period, and there will be a 1-week follow-up period for all participants. A further 1-week follow-up will take place 3 months after completion of the intervention.



Intervention

Each participant will receive 30-minute daily sessions of the BCI-N intervention for 20 days over a 4-week period in their home. Each session will involve two 15-minute BCI-N interventions divided by a 5-minute break, and each session will start and finish with measurement of the resting-state EEG levels. The BCI-N treatment incorporates an interactive gaming interface (ie, NeuroGame), and a neuromodulation protocol targeted to suppress theta and low alpha (4-8 Hz) and high beta (20-30 Hz) band powers and to enhance high alpha (9-12 Hz) band power (Figure 2). We will acquire the EEG using the EEG system SMARTING device (mBrainTrain; see Figure 2). During the BCI-N intervention, neurofeedback will be provided on SCI neuropathic pain-related regions of the brain, such as C3 and C4 [24]. In particular, the EEG signals will be processed in real time with custom scripts in MATLAB R2020b (MathWorks) using EEGLAB [43] functions. The real-time EEG processing will include extracting the power from the frequencies of interest (ie, 4-8 Hz, 9-12 Hz, and 20-30 Hz) and transferring the information to the NeuroGame interface. The NeuroGame interface was developed using the Unity 3D game engine (Unity Technologies 2019.2.6f1). Our game scenario is based on an online game called A Waffles Fate [44]. We modified the concept from a navigating ghost to a jellyfish. Our scenario, called Floating Jellyfish, provides neurofeedback in an interactive, goal-directed, virtual gaming environment. The visual feedback of the Floating Jellyfish game scenario is as follows: When only 1 EEG frequency band power is suppressed or reinforced as desired, the jellyfish changes color; when 2 frequency band powers are activated correctly, the jellyfish starts to move; and when all 3 band powers are activated, the ocean background changes color, and a seconds timer begins. Points accumulate only for those seconds that the participant keeps all 3 bands activated. The aim of the game is to receive as many points as possible. Points are summed across each 30-minute daily session of BCI-N treatment. Furthermore, the total points scored will be summed across all 20 sessions of BCI-N treatment, with the aim being to accrue as many points in total as possible. The within- and between-session points totals will also provide valuable information about the participants' experience, engagement, and progression through the game.

Figure 2. Neurofeedback loop of the brain-computer interface-based neuromodulative intervention (Floating Jellyfish). EEG: electroencephalogram.



Outcome Measures

Primary Outcome Measure

The VAS will serve as the primary outcome measure of SCI neuropathic pain. We will ask the study participants to rate the average intensity of pain during 3 specific epochs each day, using a VAS. The VAS is a 10-cm horizontal line with "No Pain" at one end and "Maximum Pain Imaginable" at the other end. Respondents are asked to make a mark along the line that represents their pain intensity. At 12 o'clock (noon), participants will rate the average intensity of the pain they experienced from the time they woke up that day until noon. At 6 PM, they will rate their average pain intensity between noon and 6 PM. Finally, at the time they go to bed, they will rate the average of the pain intensity they experienced between 6 PM and the time they went to bed. The mathematical average of the 3 ratings will then be computed to represent that participant's average daily pain intensity. If any ratings are missing, the score will be the average of the ratings obtained. Although consensus groups recommend the numeric rating scale over the VAS in pain clinical trials because some individuals have problems with understanding the VAS [45], we chose the VAS because our experience with the SCI population is that they prefer it over the numeric rating scale. Indeed, a great deal of evidence supports the reliability and validity of the VAS for assessing pain intensity among individuals who are able to use this measure [46]. Participants will complete this daily paper-and-pencil pain diary during all 3 phases; that is, the baseline (7, 10, or 14 days), intervention (20 days), and follow-up (7 days) phases.

Secondary Outcome Measure

Pain interference will serve as a secondary outcome measure. We will assess the degree of pain interference by 6 items from the Brief Pain Inventory (BPI) [47]. These items will assess general activity, normal work, relations with other people, enjoyment of life, mood, and sleep on a scale of 0 to 10 (0 = "does not interfere" and 10 = "completely interferes"). Degree of pain interference will be assessed daily in the evenings during the baseline, intervention, and follow-up phases.

We will have daily contact with the participants, both to address any questions they may have about the VAS and BPI measures, and to ensure they are completing their pain diaries and BPIs during the times they are supposed to.

Generalization Measures

We will collect generalization measures to evaluate whether the effect of the treatment extends beyond improvements in the primary and secondary outcomes [37]. For example, in this study, measures will be administered to assess whether any treatment effects generalize to behaviors and outcomes other than the pain intensity and pain interference. The generalization measures are important to strengthen the external validity of the research findings [37]. In this study, these measures will include resting-state EEG, neuroimaging data (in this case, thalamic GABA content), and psychological questionnaires measuring levels of anxiety and depression, quality of life, well-being, and sleep quality.

We will administer the psychological questionnaires at 5 time points: (1) prior to the baseline phase, (2) on the last day of the baseline phase, (3) on the last day of the intervention phase, (4) on the last day of the first follow-up phase, and (5) on the last day of the second follow-up phase. We will collect the resting-state EEG and the neuroimaging data at 2 time points: prior to and following completion of the intervention.

Psychological Questionnaires

Participants will complete the 36-item Short Form Health Survey modified for SCI (SF-36 walk-wheel) [48], the COMPAS-W Scale of Wellbeing [49], the State Anxiety Inventory (SAI) [50], the Beck Depression Inventory (BDI) [51], and the Medical Outcomes Study Sleep Scale (MOS-SS) [52]. These questionnaires are self-report measures. The SF-36 [48] is a frequently used instrument that measures global health-related quality of life. The SF-36 [48] consists of 8 scales: physical functioning, physical role functioning, bodily pain, general health perceptions, vitality, social role functioning, emotional role functioning, and mental health. Higher scores represent a better health status. The 26 items of the COMPAS-W [49] scale measures both subjective and psychological well-being. It consists of 6 subscales, which provide an indication for different aspects of well-being: composure, own worth, mastery, positivity, achievement, and satisfaction. Higher scores represent higher levels of well-being. The 20-item SAI [50] assesses state anxiety, with higher scores indicating greater anxiety. The 21-item BDI [51] is used to assess the severity of depressive symptoms, with a higher score indicating a greater number of depressive symptoms. The 12-item MOS-SS [52] assesses 6 key factors of sleep: sleep initiation, maintenance, respiratory problems, quantity, perceived adequacy, and somnolence. Higher scores reflect more sleep quality and quantity. Lastly, we will use the Neuropathic Pain Scale (NPS) [53] to evaluate the specific qualities of SCI neuropathic pain, such as sharp, hot, dull, cold, and sensitive.

Resting-State EEG Measures

We will record resting-state EEG with the participants' eyes closed (3 minutes) and eyes open (3 minutes) using the 24-channel EEG device SMARTING. The electrode placements are according to the standard 10-20 locations. The electrode impedance will be kept under 5 kΩ, and the sampling frequency will be 500 Hz.

Neuroimaging Measures

Participants will lie supine, headfirst, on the bed of a 3-T magnetic resonance imaging machine (Ingenia; Philips) with their head immobilized in a 32-channel head coil. We will use multiplanar (axial, sagittal, coronal) reformats for voxel placement. GABA-edited Meshcher-Garwood Point Resolved Spectroscopy (MEGA-PRESS) [54] will be acquired from a voxel ($2\times2\times2$ cm^3), which will be centered in the contralateral (to pain) thalamus in each participant.

Safety, Feasibility, and Experience Measures

We will collect participants' feedback regarding perceived safety and feasibility of the intervention following each session of BCI-N treatment using study-specific questions (qualitative

data). Following the completion of 20 sessions of BCI-N treatment, the participants will complete the Usefulness, Satisfaction, and Ease of Use [55] questionnaire and the Patient Global Impression of Change [56] scale to assess the feasibility and perceived change in pain, respectively. Additionally, we will conduct an unstructured interview after completion of the intervention to assess each participant's experience with the BCI-N system and the mental strategy or strategies they used during neurofeedback. The topics that will be addressed will include ease of use, barriers to utilization, participant burden, technology acquisition, and individualized mental strategy. We will use the information gathered from the unstructured interviews to optimize the technological design, clinical protocols, and assessment procedures for subsequent larger trials.

Data Analysis

Primary and Secondary Outcomes Analysis

We will analyze primary and secondary outcomes separately based on the SCED analysis. The SCED analysis mainly relies on visual inspection. However, we will inspect and analyze the outcome measures from this study using both visual analysis and supplementary statistical analysis [57]. In the visual analysis, the baseline phase establishes a benchmark against the intervention phase to investigate any natural change in the outcome of interest. We will use a structured analysis to investigate whether the treatment-induced changes in the primary and secondary outcomes are reliable and consistent across participants [57,58].

The data across all phases will be scattered and visually analyzed using both within-phase and between-phase analyses [35,59]. Within-phase analysis refers to evaluating the data patterns in each phase, and between-phase analysis evaluates the data overlap between phases and the data pattern consistency across participants. To decide whether and to what extent the intervention has had an effect on the primary and secondary outcome measures, multiple factors need to be considered in interpreting the data: (1) trend, (2) level, (3) stability, (4) consistency, and (5) overlap.

Trend refers to the slope of changes across observations (over time), which we will estimate using the split-middle method [59]. This method is robust to the effects of the autocorrelation of the data. Autocorrelation is the similarity between observations as a function of time, which we will estimate using the delta-recursive method [60].

Level refers to the rate of change either within a phase or from one phase to the next phase [59]. The between-phase relative level change is the proportional change from the last half of the baseline to the first half of the intervention phase, whereas the absolute level change is the immediacy of change from the last session of the baseline to the first session of the intervention using median values.

Stability refers to the percentage of data points on or within a stability envelope. We will evaluate the stability envelope of the baseline phase by a criterion of 80% of data points being within 25% of the median value [59]. A requirement for demonstrating an effect of the intervention is the stability of the baseline phase compared with the intervention phase.

Consistency refers to the extent that data patterns of the same phase are similar across participants (eg, consistency of the baseline phase between participants). We will evaluate this by the consistency of data patterns approach. In addition, we will apply the consistency of the effects to assess the replication of the between-phase change across participants [61].

Overlap is the percentage of data points from the intervention phase that overlap with the data from the baseline phase. The higher percentage of nonoverlap data determines a larger intervention effect. Nonoverlap indices are more robust than indices of mean or median level changes across phases. Nonoverlap methods do not rely on means or medians, but rather consider the individual values of all data points in pairwise comparisons across phases [62]. These methods are distribution free, meaning that they do not require parametric assumptions.

One of the most robust nonoverlap methods is the Tau effect size [63,64], which is based on the pairwise comparison. Pairwise comparison between 2 measures is determined to be concordant (positive), discordant (negative), or tied [63,65]. In a concordant pair, there is an increase between 2 measures; in a discordant pair, there is a decrease; and in a tied pair, both measures are equal. Tau is calculated using the formula  , where S is the Kendall rank correlation score, calculated as $n_c - n_d$ (number of discordant pairs subtracted from the number of the concordant pairs), and n_{pairs} is the number of all pairs.

Tau-U effect size [63,65] extends Tau in an attempt to control for the undesirable trend in the baseline phase by estimating and removing it. A SCED with AB design consists of both within-phase (A-to-A, B-to-B) and between-phase (A-to-B) pairwise comparisons. A-to-A and B-to-B comparisons characterize the trend within phase A and phase B, respectively, and A-to-B comparisons describe the difference between phase A and phase B. To remove the within-phase trend from the between-phase difference, we will use the following formula:

We will use Tau-U to provide an overall treatment effect size across the 3 participants.

Generalization Measures Analysis

Psychological Questionnaires

We will calculate and extract total scores and subscores of the psychological questionnaires (SF-36 walk-wheel [48], COMPAS-W [49] SAI [50], BDI [51], MOS-SS [66], and NPS [52]) for further analysis (see the Reliable Change Index subsection below).

Resting-State EEG

We will analyze resting-state EEG data using custom scripts based on the EEGLAB toolbox [43] functions in MATLAB. We will apply a band-pass filter (1-30 Hz) to the EEG data after downsampling to 250 Hz. Then, the EEG data will be rereferenced to the average of all 24 electrodes. We will use an artifact subspace reconstruction [67] method with default

parameters for denoising and removing movement artifacts. Subsequently, we will use power spectral density to estimate the intended frequency band powers (ie, theta, alpha, and high beta) from the cleaned data. Finally, we will extract the frequency band power values for further analysis (see Reliable Change Index below).

Neuroimaging

We will analyze the acquired spectra using the Java-based magnetic resonance user interface (jMRUI version 6.0; MRUI Consortium). First, we will remove the dominant water resonance using the Hankel Lanczos singular valve decomposition algorithm. The ON and OFF spectral subsets will be summed, producing single ON and OFF 68-ms subspectra for each spectra dataset. These 68-ms subspectra will then be subtracted, resulting in GABA-edited difference spectra to measure GABA concentration at 3.01 ppm. We will quantify GABA using AMARES, a nonlinear least-squares fitting algorithm operating in the time domain. Peak fitting for GABA will be performed after manually defining the center frequency and line width of the GABA peak and modelling the GABA peak as a singlet. We will use Lorentzian curves to obtain the peak amplitude for this resonance. The OFF spectral subsets will be summed, producing single OFF 68-ms subspectra for each spectra dataset to measure creatine concentration at 3.02 ppm. We will then phase the single OFF 68-ms subspectra with respect to both the zero- and first-order phase. Spectral fitting in AMARES will be performed after manually defining the center frequency and line width of the creatine peak and modelling the creatine peak as a singlet. We will use Gaussian curves to obtain the peak amplitude for this resonance. Lastly, the GABA to creatine ratios will be calculated and extracted for further analysis (see Reliable Change Index below).

Reliable Change Index

We will evaluate changes in generalization measures such as power spectral density, GABA to creatine ratios, and total scores and subscores of the psychological questionnaires using the Reliable Change Index (RCI) [68,69]. We will use the RCI to evaluate the reliability of change over time for individual data. This index indicates whether the change score between 2 time points (eg, pre- and postintervention) for the same individual is considered clinically significant.

RCI is a ratio of the actual observed difference by the standard error of the difference (SE_{diff}): $RCI = [M_{post} - M_{pre}]/SE_{diff}$, and $SE_{diff} = SD\sqrt{2}(1 - r)$, where SD is the standard deviation of the measurement and r is the reliability coefficient of the measure.

Results

This clinical trial has been approved by the University of New South Wales Human Research Ethics Committee (approval number: HC190411) and the University of Technology Sydney Human Ethics Committee (approval number: ETH19-4090). Additionally, this study is registered through the Australian and New Zealand Clinical Trials Registry (registration number: ACTRN12620000556943). We plan to commence the trial in October 2020 and expect to publish the results by the end of 2021.

Discussion

Overview

Preliminary data in support of BCI-N treatment for SCI neuropathic pain have been reported [24,26]. However, further studies are needed to provide more definitive evidence of the effectiveness of this intervention. This clinical trial using SCED methodology has been designed to evaluate the effectiveness of a novel BCI-N treatment for people with neuropathic pain after SCI.

The BCI-N system of this study will address a key limitation of previous EEG neurofeedback interventions, which have mostly relied on a single form of virtual interaction [20,22,24]. Studies have shown greater cortical involvement [32] and pain reduction [28-31] during the interactive engagement with multiple gaming scenarios than with 1 form of virtual interaction. Based on this evidence, we will use a self-developed BCI-N treatment, which consists of 3 interactive virtual scenarios in a goal-directed gaming environment. Further, the BCI-N system used in this study can provide neurofeedback simultaneously on different brain regions, and hence can be individualized to each participant's needs. For example, for a participant with bilateral pain, both C3 and C4 EEG channels can be targeted, whereas for a participant with unilateral pain, only C3 or C4 will be targeted during the BCI-N intervention. Additionally, the reinforcement and suppression criteria (ie, the baseline thresholds) for the targeted frequency bands can be customized according to the participant's progress during the intervention. For example, we can change the difficulty of the game by modifying the baseline thresholds as a way to increase motivation.

SCED is a powerful design to establish guidelines for evidence-based interventions [35]. The key to the SCED method with multiple baselines is that the intervention is introduced in a staggered sequence [35], and the outcome of interest, that is, average pain intensity, is measured repeatedly during different phases. The staggered introduction of the intervention allows for drawing conclusions regarding intervention effects distinct from those associated with maturation, experience, learning, or practice [70]. The SCED methodology accounts for potential confounders, such as environment factors, which may affect primary and secondary outcome measures. Unlike traditional group designs, a SCED can address the effects of the intervention at the individual's level in a controlled and unbiased way by randomly allocating different baseline periods across participants.

Investigating our novel self-developed BCI-N intervention with a SCED and evaluating it with visual and statistical analyses will provide a rigorous methodology for this study. The high internal validity of a well-implemented SCED study allows for the results of the data analyses to draw reliable conclusions about the effectiveness of the intervention [42,71]. Experimental control is established when the effects of the intervention are repeatedly and reliably demonstrated within a single participant or across a small number of participants. In the multiple-baseline design, each participant will be their own control and will provide an instance of the intervention's effect replication. This

within-study replication is the basis of internal validity in SCEDs. By replicating an investigation across different participants, the generalization of the intervention effects can be examined and hence potentially increase the external validity [35]. Additionally, SCEDs are ideal for researchers working with small or very heterogeneous populations in the development and implementation phases of novel research studies. Thus, the SCED with multiple baselines is considered a viable alternative approach to randomized clinical trials for demonstrating the effectiveness of an intervention when the recruitment of large samples is not feasible. [42].

Limitations

The SCED trial with multiple baselines will not be able to demonstrate effectiveness of the BCI-N treatment if 1 of the 3 participants drops out during the baseline or intervention phases. To address this limitation, we will perform a mock BCI-N treatment session for each participant prior to commencement of the trial in order to increase compliance and ensure a high comfort level of the EEG headset, a comprehensive understanding of the treatment protocol, assessment procedures, and performance of gameplay during the neurofeedback session.

Authors' Contributions

SMG, NH-S, and TN-J designed the clinical trial and wrote the manuscript. SMG, NH-S, TN-J, C-TL, CATC, AKS, and T-TND developed the game interface and signal processing algorithms. All authors critically revised the manuscript and approved the final manuscript.

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Conflicts of Interest

None declared.

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Abbreviations

BCI: brain-computer interface
BCI-N: BCI-based neuromodulative
BDI: Beck Depression Inventory
BPI: Brief Pain Inventory
EEG: electroencephalography
GABA: γ-aminobutyric acid
MEGA-PRESS: Meshcher-Garwood Point Resolved Spectroscopy
NPS: Neuropathic Pain Scale
RCI: Reliable Change Index
SAI: State Anxiety Inventory
SCED: single-case experimental design
SCI: spinal cord injury
SCRIBE: Single-Case Reporting Guideline in Behavioural Interventions
SF-36: 36-item Short Form Health Survey
VAS: visual analog scale

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Protocol

The Design of a Randomized Clinical Trial to Evaluate a Pragmatic and Scalable eHealth Intervention for the Management of Gestational Weight Gain in Low-Income Women: Protocol for the SmartMoms in WIC Trial

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Abstract

Background: Less than one-third of women gain an appropriate amount of weight during pregnancy, which can influence the long-term health of both the mother and the child. Economically disadvantaged women are the most vulnerable to maternal obesity, excessive weight gain during pregnancy, and poor birth outcomes. Effective and scalable health care strategies to promote healthy weight gain during pregnancy specifically tailored for these women are lacking.

Objective: This paper presents the design and protocol of a biphasic, community-based eHealth trial, SmartMoms in WIC, to increase the adherence to healthy gestational weight gain (GWG) recommendations in low-income mothers receiving women, infant, and children (WIC) benefits.

Methods: Phase 1 of the trial included using feedback from WIC mothers and staff and participants from 2 community peer advisory groups to adapt an existing eHealth gestational weight management intervention to meet the needs of women receiving WIC benefits. The health curriculum, the format of delivery, and incentive strategies were adapted to be culturally relevant and at an appropriate level of health literacy. Phase 2 included a pragmatic randomized controlled trial across the 9 health care regions in Louisiana with the goal of enrolling 432 women. The SmartMoms in WIC intervention is an intensive 24-week behavioral intervention, which includes nutrition education and exercise strategies, and provides the technology to assist with weight management, delivered through a professionally produced website application.

Results: Phase 1 of this trial was completed in July 2019, and recruitment for phase 2 began immediately thereafter. All data are anticipated to be collected by Spring 2023.

Conclusions: The SmartMoms in WIC curriculum was methodically developed using feedback from community-based peer advisory groups to create a culturally relevant, mobile behavioral intervention for mothers receiving WIC benefits. The randomized clinical trial is underway to test the effectiveness of a sustainable eHealth program on the incidence rates of appropriate GWG. SmartMoms in WIC may be able to offer an innovative, cost-effective, and scalable solution for GWG management in women served by WIC.

Trial Registration: ClinicalTrials.gov NCT04028843; https://clinicaltrials.gov/ct2/show/NCT04028843

International Registered Report Identifier (IRRID): DERR1-10.2196/18211

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KEYWORDS

mobile health; mobile phone; maternal obesity; gestational weight gain; community health

Introduction

Pregnancy is a critical time that influences the immediate and long-term health of both the mother and the child. The health and nutritional status of women before pregnancy is arguably the most important factor for long-term health outcomes [1]. Additionally, the nutritional status of women during pregnancy, including gestational weight gain (GWG), influences birth outcomes, maternal and infant health, and long-term risk for chronic disease in mothers [2] and children [3,4]. Fewer than one-third of women gain an appropriate amount of weight throughout pregnancy [5].

Women who are economically disadvantaged are the most vulnerable to inappropriate weight gain during pregnancy [6,7] and poor birth outcomes [8-11]. According to the US Census Bureau in 2015, more than 1 in 8 women and 1 in 4 children live in poverty [12]. The US Department of Agriculture's Supplemental Nutrition Assistance Program for Women, Infants, and Children (WIC) was established to safeguard the health of low-income pregnant women, infants, and children up to the age of 5 years who are at nutritional risk. Data from the Centers for Disease Control Pregnancy Risk Assessment Monitoring System report that at least 50% of pregnant women supported by WIC have overweight or obesity [13], and only 30% of the women achieve appropriate GWG [14]. The WIC program has an established framework across the United States and provides services to approximately 15% of pregnant women each year [14]. WIC therefore has a unique opportunity to disseminate a weight management program to millions of pregnant women most in need of such programs. Effective and scalable community-based interventions specifically tailored to underserved women are urgently needed.

Pragmatic clinical trials testing scalable, culturally relevant, and appropriately powered interventions aimed at promoting healthy GWG in economically disadvantaged pregnant women are lacking. The SmartMoms in WIC trial will address these gaps by developing and evaluating the effectiveness of an eHealth intervention on the incidence of appropriate GWG in economically disadvantaged mothers receiving WIC benefits. The state-wide randomized controlled trial will test the central hypothesis that relative to WIC participants receiving usual care, participants receiving the newly formed Healthy Beginnings program will have greater adherence to the 2009 Institute of Medicine (IOM; now Academy of Medicine) GWG guidelines and significant improvements in physiological and behavioral factors. The aim of this paper is to describe the development, methodology, and recruitment plan of the SmartMoms in WIC trial.

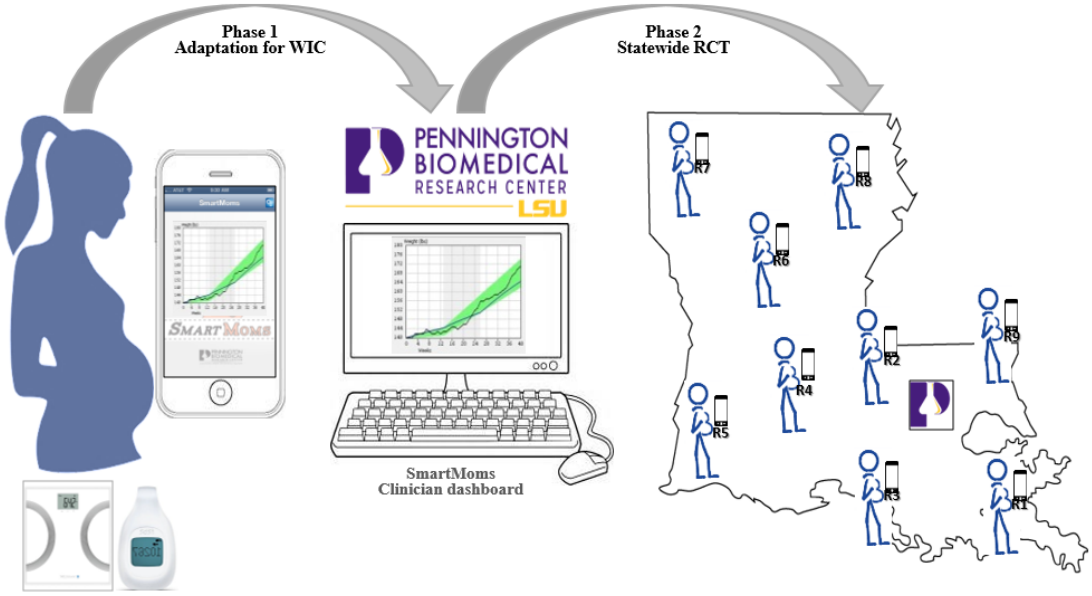
Methods

Study Design

A pilot trial conducted at Pennington Biomedical Research Center (PBRC) in Baton Rouge, Louisiana, showed the efficacy of SmartMoms, an intensive behavioral smartphone intervention to reduce excess GWG in pregnant women with overweight or obesity when compared with delivery via a traditional in-person approach [15]. Notably, as compared with SmartMoms delivered in person, women receiving SmartMoms through a smartphone were more adherent (76.5% vs 60.8%). This trial also showed that a GWG intervention is more cost-effective when delivered through a smartphone device compared with delivery via in-person sessions (smartphone: US $97, SD US $6 vs in person: US $347, SD US $40). In response to the US National Institutes of Health solicitation for research focused on Maternal Nutrition and Pre-pregnancy Obesity: Effect on Mothers, Infants, and Children (PA-18-135), we developed a randomized controlled trial titled: *A pragmatic, scalable e-health intervention for management of gestational weight gain in low-income mothers (SmartMoms in WIC)*. The clinical trial is registered at ClinicalTrials.gov (NCT04028843). This work is supported by the National Institutes of Health (R01NR017644) and core support via U54GM104940 and P30DK072476.

The SmartMoms in WIC study has 2 phases. Phase 1 includes formative research that informs the enhancements made to the previous SmartMoms intervention to better meet the needs of economically disadvantaged women supported by WIC during pregnancy. Phase 2 includes the execution and completion of a state-wide randomized controlled trial. Phases 1 and 2 are depicted in Figure 1. The study is accomplished through close collaboration with the Louisiana Department of Health; Louisiana Special Supplemental Nutrition Program for Women, Infants, and Children; and engagement with 2 community stakeholder groups: Baton Rouge Community Advisory Board of the Louisiana Clinical and Translational Sciences Center (LA CaTS) and a newly formed WIC Mothers' Advisory Group.

Figure 1. Two phases of the SmartMoms in WIC Trial.



Phase 1

For phase 1, the specific aim was to use data from formative research surveys of 614 WIC clients and staff from across Louisiana together with semistructured interviews and consultations with a Community Advisory Board and a WIC Mothers' Advisory Group to adapt SmartMoms for economically disadvantaged women.

Adaptation of the SmartMoms Intervention for Low-Income Women

A state-wide qualitative research study (NCT02657577) [16] was conducted as formative research to understand whether WIC would be a suitable venue for SmartMoms and how it should be customized considering the needs and barriers of WIC clients. A random sample of WIC clinics in each of the 9 regions (1-2 clinics per region) for the Louisiana Department of Health was chosen for the surveys. The survey was designed to understand the desire for weight management to be incorporated into WIC services. Results showed that WIC clients and WIC staff at the state, regional, and clinic levels stated that weight management is an important service for WIC. Furthermore, 76% (318/419) of clients expressed a desire to lose weight, and >70% stated they would like to receive weight management services, including cooking classes, support groups, and additional nutrition or lifestyle information through a free app or website. For clients who reported difficulty attending WIC appointments, lack of transportation and time restraints were identified as the primary barriers. In addition, 78% (152/195) of the WIC staff surveyed stated that weight management is needed in WIC. However, WIC staff stated that more time with the client would be needed to adequately implement a weight management program. The survey findings demonstrate that an intervention geared toward weight management in WIC should be accessible through smartphone or internet-based apps as recommended by clients and outside of the WIC appointment to eliminate burden from WIC staff.

Using the results of the WIC survey as a starting point, phase 1 engaged 2 independent stakeholder groups: the Baton Rouge Community Advisory Board of LA CaTS and a newly formed WIC Mothers' Advisory Group to guide the adaptation of the piloted curriculum of the SmartMoms intervention [15] specific to the wants and needs of economically disadvantaged women. Monthly meetings were held with both groups to produce a curriculum that was more relatable to pregnant women receiving WIC, culturally sensitive, and at an appropriate level of health literacy.

On the basis of the recommendations provided by the WIC Mothers' Advisory Group, we developed a mechanism for social support, modified the written intervention content to be delivered via short videos, incorporated WIC-approved foods in all dietary materials, produced exercise videos featuring pregnant women, and developed a gamification incentive program. Advisory Group recommendations and the resulting intervention modifications are shown in Table 1.

The Community Advisory Board and the WIC Mothers' Advisory Group also named the usual care and intervention groups. Usual care participants are enrolled in the *WIC Nutrition* group as all nutrition information is provided through WIC standard care, and the participants receiving the SmartMoms in WIC intervention are enrolled in the *Healthy Beginnings* group.

The advisory boards recommended that women in the usual care group would also benefit from receiving reputable health information throughout pregnancy. Existing health materials unrelated to diet, exercise, and weight gain throughout pregnancy, such as from the American Academy of Pediatrics, are shared with usual care participants once per week for 24

weeks. The weekly curriculum topics of the Healthy Beginnings intervention and usual care groups are shown in Table 2.

Table 1. Weekly content for the intervention and control groups.

Advisory Board recommendations	Resulting modification to the Healthy Beginnings interventions
Mechanism for social support	Advisory Group participants wanted a sense of community within the programs. Virtual support groups were created through Facebook. Separate and private groups were created for intervention and usual care groups.
Video-based content	Short, 2 to 4 min videos were professionally produced to deliver intervention lessons to participants.
Relatable recipes	Research dieticians developed 24 recipes that incorporate WIC[a]-eligible foods. Preparation of these recipes are demonstrated in full length (n=10) and fast forward videos (n=14).
Exercises for pregnant women	8 coach-led group exercise classes were produced along with 24 *exercise of the week* videos. All exercise materials are suitable for women to perform safely throughout pregnancy.
Gamification program to incentivize mothers	Mothers wanted to earn points for intervention adherence. The Mommy Market was developed so that participants in the intervention could earn points from demonstrating an understanding of intervention content and redeem points for pregnancy and infant-related products at the Mommy Market.

[a]WIC: women, infants, and children.

Table 2. Weekly content for the control and intervention groups.

Week	Healthy Beginnings	Usual care
1	Weight gain in pregnancy	Prenatal vitamin
2	Overcoming barriers to success	Sleep
3	Meal planning and grocery shopping	Preparing for labor and birth
4	Meal prep and healthy cooking	Healthy attachment
5	Portion control and eating patterns	Recommended immunization schedules
6	Behavior chains	Tooth decay in infants
7	Controlling food cues and hunger	How to take a child's temperature
8	Building social support	Meditation for children
9	Emotional eating	Generosity in children
10	Gestational diabetes	Insect repellant
11	Protein and fat	Conflict resolution
12	Fluids and fiber	Childproofing the home
13	Carbohydrate and sugar	Cell phones
14	Prenatal vitamins	Child safety
15	Social eating	Infant learning
16	Physical activity	Car seats
17	Mindfulness and relaxation	Parenting an infant
18	Managing food cravings and snacking	Postpartum depression
19	Healthy eating on the go	Breastfeeding
20	Stress and sleep	Choosing a pediatrician
21	Postpartum depression	Back to sleep, tummy to play
22	Preparing for labor and birth	Poison safety
23	Breastfeeding	Preparing for baby
24	Optimizing health postpartum	Parenting

Phase 2

The specific aim of phase 2 is to conduct a randomized controlled trial within Louisiana WIC clinics across the state to test the effectiveness of the Healthy Beginnings intervention on adherence to the 2009 IOM weight gain in pregnancy guidelines. The primary hypothesis is that compared with WIC participants receiving usual weight management care,

participants receiving the Healthy Beginnings intervention will have greater adherence to the 2009 IOM weight gain in pregnancy guidelines and significant improvements in physiological and behavioral factors.

The primary outcome is the incidence of adherence to the 2009 IOM guidelines for GWG per week across the second and third trimesters [17]. The starting weight is the participant's weight measured between 10^0 and 15^6 weeks at visit 1. The final pregnancy weight is measured between 35^0 and 37^6 weeks at the late pregnancy study visit. The rate of weight gain is equal to the final pregnancy weight minus the starting weight divided by the number of weeks between the 2 measurement dates. According to the 2009 IOM recommendations, the appropriate rate of weight gain in trimesters 2 and 3 is 0.35-0.50, 0.23-0.33, and 0.17-0.27 kilograms per week for women with normal weight, overweight, and obesity, respectively.

The main secondary outcomes (Table 3) include the rate of GWG (kilograms per week), maternal diet, physical activity, quality of life and stress, birth outcomes, WIC food voucher redemption rate, and postpartum weight retention. Subgroup analyses are planned for intervention effects within BMI categories (normal weight, overweight, and obesity) and race or ethnicity, and for women enrolled in Healthy Beginnings, subgroup analyses include intervention adherence.

Table 3. SmartMoms in WIC primary and secondary outcomes.

Outcomes	Outcome descriptions
Primary outcome	• Incidence of adherence to the 2009 Institute of Medicine's guidelines for gestational weight gain for normal weight, overweight, and obesity pregnant women
Secondary outcomes	• Gestational weight gain per week • Maternal diet • Physical activity • Quality of life and stress • Birth outcomes • WIC[a] food voucher redemption rate • Postpartum weight retention at 1 year

[a]WIC: women, infants, and children.

Study Population

The trial aims to enroll 432 pregnant women certified to receive WIC benefits during their current pregnancies, evenly from the 9 WIC regions in Louisiana. Eligibility criteria were established to include a broad range of healthy pregnant women. Inclusion criteria include singleton viable pregnancy, prenatal certification to receive WIC benefits for the current pregnancy (by meeting income requirements mandated by WIC), gestational age <15 weeks at screening, BMI between 18.5 and 40.0 kg/m^2 using the prenatal WIC certification visit weight, having a smartphone with internet access, and be willing to be identifiable to other study participants in the program because of social interaction via social media. Exclusion criteria include maternal age between <18 and >40 years at screening; current drug, tobacco, or alcohol use; nonpregnancy illness (HIV, cancer, heart disease, or type 1 or type 2 diabetes), hypertension at screening (systolic blood pressure [SBP]>160 mm Hg or diastolic blood pressure [DBP]>110 mm Hg), current mental health or eating disorder, and plans to move out of the state during the study time frame. Furthermore, participants could be excluded after the screening visit if they failed to complete a behavioral run-in task of keeping a food and activity diary with 80% compliance.

Trial Personnel

The study organization involves 2 teams of personnel: a clinical assessment team and an intervention team. The clinical assessment team consists of trained maternal and infant research specialists employed by Pennington Biomedical. The clinical assessment team staff are present in the WIC clinics to recruit, screen, and consent participants, conduct study visits, and obtain outcome assessment data. The intervention team are trained behavioral health coaches located at the study hub in Baton Rouge, Louisiana. The health coaches randomize participants, manage social support groups, and oversee intervention delivery via the eHealth system [18]. The study investigators and clinical assessment team are blinded to the treatment group assignment until the end of the research trial.

Recruitment and Randomization

Our randomized controlled trial to test the effectiveness of the Healthy Beginnings intervention began in July 2019. The trial is conducted in partnership with the Louisiana Department of Health and participating WIC clinics throughout the state of Louisiana. The study protocol was approved by the Institutional Review Boards at Pennington Biomedical Research Center (PBRC) and the Louisiana Department of Health.

Participants are recruited from participating WIC clinics dispersed across 9 regions of the Louisiana Department of Health at their prenatal WIC certification visits (Figure 1). The trial received endorsement of the Governor of Louisiana, Secretary for Health, and State WIC Director. The State WIC Director and regional nutritionists helped to identify WIC clinics to collaborate in the trial. A memorandum of understanding was established with each partnering clinic after space and number of monthly WIC pregnancy certifications were confirmed.

Participants are recruited by clinical research staff in person, by referrals from WIC staff, or by posting flyers in client waiting lobbies. Interested participants complete an initial web-based eligibility survey, which collects contact information and asks the participant basic questions regarding their health history

and anthropometrics. If the participant satisfies the basic eligibility criteria (ie, gestational age, singleton pregnancy, age, BMI), they are scheduled for a screening visit to obtain written informed consent and determine eligibility to participate in the trial.

Randomization occurs after the first study visit, but before the participant reaches the 17th week of pregnancy to ensure that the program is initiated by the end of the 16th week of pregnancy. The randomization schedule is prepared by a biostatistician and is not revealed to the clinical research team.

Intervention Goals, Approach, and Rationale

The Healthy Beginnings intervention is a 24-week intensive behavior modification program now customized for pregnant women receiving WIC that seeks to promote healthy GWG through self-monitoring of weight and activity data, automated prescriptive feedback from the mobile app, and personalized feedback from health coaches. All interactions and treatment recommendations between the participant and the health coaches occur remotely via the multimedia functions of a smartphone or computer.

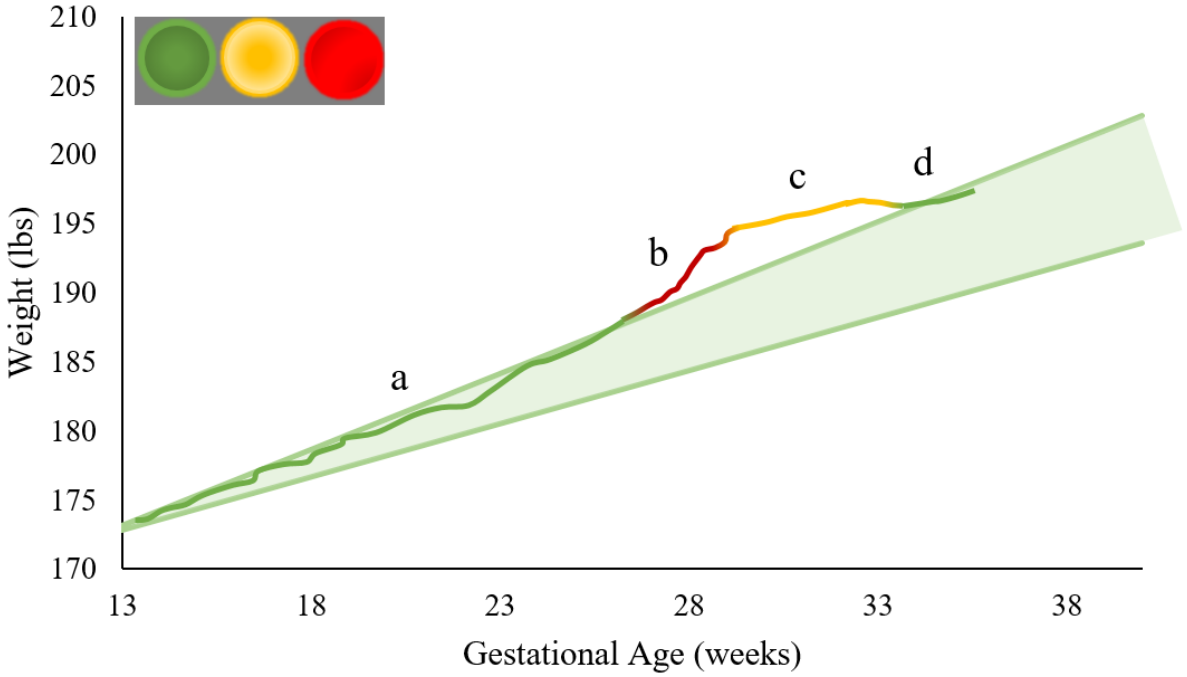
Following randomization, participants in the Healthy Beginnings intervention group are mailed a startup kit, which includes a Fitbit (Fitbit Alta), a cellular-enabled scale (Bodytrace), and instructions on how to use and synchronize the devices and access the Healthy Beginnings app. Participants are instructed to weigh daily, wear the Fitbit throughout their pregnancy, and to synchronize the Fitbit device periodically. These data are automatically and wirelessly transmitted to a clinician and participant dashboard in near real time, where the weight and activity data are automatically plotted on the weight graph and step graph, dynamic charts within the Healthy Beginnings intervention app.

Weight Component

Body weight data are displayed on the participants' personalized weight graph and in relation to their recommended weight change trajectories within the app. An example of the weight graphs is presented in Figure 2. Participants are considered adherent to their personalized weight recommendations if their body weight tracks within the range established by the 2009 IOM guidelines throughout the intervention [19]. Therefore, body weight is used to quantify and depict adherence to the dietary intake goals and to deliver more intensive treatment. Participants are taught that adherence to their weight and activity graphs will promote healthy GWG, but deviation above or below the IOM target guidelines warrants a corresponding change in diet and physical activity. The weight and activity graphs provide participants with automated prescriptive feedback. The feedback includes treatment recommendations bolstered on behavior change theories when participants are out of range (weight or activity level) or congratulatory messages with strategies to maintain success when the weight and activity goals are being met. For added visual feedback, the app automatically generates color-coded visual cues displayed on the graphs indicating whether weights are within the IOM zone of adherence (green), out of the IOM zone (red), or out of the IOM zone but changing at a rate that reflects adherence to the weight gain target (yellow).

When body weight is repeatedly outside the participants' individualized IOM zone, it serves as an objective indicator to the participant and intervention researchers that more intensive treatment strategies are needed. The intervention team meets weekly to discuss participants with body weight trajectories and adherence to the IOM weight zone. Different treatment strategies to increase the intensity of the weight management program are maintained in a toolbox. Examples of these strategies include increased frequency of contact with the assigned health coach, increased activity or exercise, adoption of a new or revised plan to self-monitor food intake using provided measuring cups to appropriately portion foods and encourage portion-controlled foods (eg, bananas, oranges, carrots, hardboiled eggs, instant oatmeal, yogurt), and advising participants to track foods consumed, which can be done with pen and paper, electronically through free web-based websites and apps, or by sending health coaches photos of their meals. The use of the toolbox strategies is tracked within the app. This toolbox approach is similar to the strategy used in the Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy (ie, the CALERIE study) [20,21] and Look AHEAD [22], and it provides a systematic and algorithmic method to improve adherence to diet and weight goals.

Figure 2. Daily weight charts and visual feedback for a. adherence to recommended rates of weight gain receives an illuminated green light as a visual cue b. above adherence to recommended weight gain receives an illuminated red light as a visual cue c. above recommended rates of weight gain but on a trajectory that is approaching recommended rates of weight gain receives an illuminated yellow light as a visual cue d. weight gain within recommended bounds once again receives an illuminated green light as a visual cue.



Physical Activity Components

A major focus of the physical activity component is on increasing lifestyle activities, such as taking the stairs, active commuting, and replacing sedentary activities with more active options. Physical activity data are collected and tracked via Fitbit and plotted on the SmartSteps graph within the app. Similar to weight graphs, automated personalized messages are deployed with added contact from intervention researchers, as needed. Both aerobic and resistance-based physical activity is encouraged each week through the *exercise of the week* and group exercise class videos.

Diet Component

Participants are encouraged to follow a healthy eating pattern as described in the 2015-2020 USDA Dietary Guidelines for Americans and use MyPlate [23]. The behavioral intervention and developed recipes encourage the intake of nutrient-dense foods including whole grains, fruits, lean protein sources, nuts, and seeds. The intervention also offers strategies to reduce or eliminate sugary drinks, desserts, and fried and rich foods and teaches MyPlate portion sizes. Participants are not required to track food intake on a daily basis; however, intervention researchers can request participants to use their smartphone camera to capture food images to be stored in the toolbox to determine the types of foods they are eating and assist with personalized coaching on the basis of their actual food intake patterns.

Intervention Details

In addition, following feedback and recommendations from the advisory boards during phase 1, the newly adapted Healthy Beginnings intervention includes a private Facebook group, a gamification incentive program, and >100 informational, exercise, and cooking videos.

Videos

There are 55 professionally produced videos to deliver intervention content and foster behavior change. Each weekly topic is broken down into 2 or 3 short lessons with supporting videos. The intervention content (Table 1) is new each week and is sent to the participant via an automated email. The email contains a summary description of the weekly topic and a website link to the short video hosted on a web-based platform (YouTube). The videos are designed to explain the topic in a simple and straightforward manner. Videos are 2- to 4-minutes long, feature pregnant women, and strongly emphasize the health benefits of the desired behavior change with regard to the health and development of their baby. In addition to the informational videos, research dietitians developed >24 recipes that incorporate WIC eligible foods and are modest in cost. The preparation of these recipes was demonstrated in either full length (n=10) or fast forward videos (n=14). Videos included variations in recipes (eg, incorporating different protein options, including vegetarian when available) and some included side dishes. Eight coach-led group exercise classes were also professionally produced along with 24 *exercise of the week* videos. All exercise materials were suitable for women to perform safely throughout pregnancy. The guided recipe and exercise videos are posted weekly and on a 24-week rotation to the Healthy Beginnings social media page.

Social Support

Participants in usual care and the Healthy Beginnings interventions are added to separate and private Facebook groups,

where interventionists lead conversations and encourage participant engagement. The intervention manager has a PhD in human clinical nutrition and holds the American College of Sports Medicine–Certified Exercise Physiologist certification. The intervention team (health coaches) hold bachelors or master's degrees in Kinesiology (fitness and human performance) or in Human Nutrition, a registered dietitian nutritionist, or certified diabetes educator certifications. The group is also monitored by an independent monitor in the Institutional Communications Department to ensure that the interactions between the interventionists and the participants remain aligned with the study objectives. The social media group of Healthy Beginnings is the platform where recipe and exercise videos are posted. The *secret* function is enabled to conceal groups and member identities from outsiders. Membership in the group occurs on a rolling basis. Once participants are enrolled into the trial, they remain in the group following birth, unless they choose to remove themselves. Thus, all women randomized can remain in their respective private Facebook groups until 1 year postpartum.

Gamification

To boost participant engagement with the intervention, we developed a gamification component. Participants earn points for engaging with health coaches, completing intervention tasks, and demonstrating behavior change. Accrued points are redeemable for pregnancy and infant-related products recommended by the advisory groups in phase 1, including diapers, bathing products, delivery robes, diaper bags, portable cribs, and strollers. Points can be redeemed for these items once per month when the *Mommy Market* store is opened. A variety of items are offered within 3-point categories of increasing value. The points required for any item are based on the goal of 70% adherence to the intervention, as this level of adherence was required to produce significant weight management results in our past eHealth study in WIC mothers [24].

Usual Care Group Strategy

Analogous with previous trials embedded in the WIC program [24,25], participants assigned to the usual care group will receive all aspects of the standard WIC program, including standard prenatal weight management advice provided by WIC staff plus a brief phone conversation to orient and bond the participant to the study. Weight management from WIC is administered through a pregnancy health pamphlet that encourages use of the American College of Obstetrics and Gynecology weight gain recommendations. To boost retention, the usual care participants also receive weekly health information unrelated to diet, physical activity, or weight management, delivered via a private Facebook group that is separate from the intervention group. Women in the usual care group receive monthly phone calls to keep participants engaged in the study.

Study Retention

For convenience, study clinic assessment visits are typically scheduled to correspond with each participant's scheduled WIC appointment. Additionally, incentives are provided to all participants on an intermittent schedule to promote engagement and improve retention of both the intervention and usual care groups. All participants are compensated US $25 at the completion of each study visit. Incentive items provided at clinic visits include measuring cups and spoons, mixing bowls, water bottles, yoga mats, hand weights and resistance bands, and a tote bag. Participants in both groups are provided the same incentive items as the clinical assessors who are blinded to the intervention assignment distribute incentives at clinic visits. Prenatal vitamins are also offered to all participants throughout pregnancy and are refilled at each prenatal clinic visit. Although incentive items are provided to participants of both groups, the schedule of incentive administration is strategically paired with intervention content. Participants in the Healthy Beginnings intervention have the ability to receive additional incentive items through the gamification component *Mommy Market*, as explained previously. Items earned through the *Mommy Market* are mailed to participants to not reveal blinding to clinic assessors.

Intervention Adherence

Adherence to the Healthy Beginnings intervention is based upon participant interaction with the weekly intervention curriculum. To receive adherence points, the participants must comment on the video or have a discussion with their health coach (via text, email, phone call, or video call) and demonstrate a basic understanding of the material. Low adherence is defined as ≤40% of session interaction, medium adherence is reaching 40.1%-70% of session interaction, and high adherence is reaching >70% of session interaction.

There are additional components of the intervention, including daily weighing and step counting, which may signify intervention adherence. However, we expect these intervention outcomes to trend similarly with the session interaction and have chosen the weekly study curriculum as the main adherence metric of the intervention as it encompasses these additional components.

Safety Monitoring

All adverse events, serious adverse events, and safety alerts are reviewed by the study medical investigator (DH) on an ongoing basis. Any significant health problems identified during the study will be referred to the participant's usual source of medical care, with her permission. Adverse events are defined as any untoward medical occurrence that may or may not be associated with participation in the study. A serious adverse event is an untoward medical occurrence, whether associated with study participation or not, which results in one of the following: death, life-threatening event, hospitalization, preterm delivery before 32 weeks of gestation, disability or permanent damage, or medication intervention to prevent permanent impairment or damage. A contraindication to physical activity during pregnancy [19] results in modification of the Healthy Beginnings intervention.

Additional safety alerts that require medical monitoring are high blood pressure (SBP≥160 mm Hg and/or DBP≥110 mm Hg) and weight loss during pregnancy. Weight loss safety alerts are BMI specific and compared with the first weight assessed in the clinic (normal BMI at enrollment: any weight loss;

overweight at enrollment: a weight loss 4%; obesity at enrollment: weight loss 6%).

Outcome Measures

Through our previous community-based trials [24], we learned that it was critical to embed clinical assessment researchers into WIC clinics as opposed to relying on WIC staff for trial implementation. Study assessments are therefore conducted at the WIC clinic by certified clinical researchers. After the screening visit, there are 6 study visits throughout the trial: 3 visits during pregnancy and 3 visits during the first year postpartum. Pregnancy outcomes are obtained before randomization at 10^0 to 15^6 weeks, approximately 12 weeks after enrollment at 24^0 to 27^6 weeks of gestation, and close to term (35^0 to 37^6 weeks). Women are followed up for 12 months after delivery, with 3 study visits occurring at 2^0 to 6^6 weeks, 6 months (22^0 to 25^6 weeks), and 12 months (48^0 to 56^6 weeks) postpartum. The assessment schedule is presented in Table 4.

Table 4. Assessment schedule.

Assessments	Screening	Early pregnancy	Mid pregnancy	Late pregnancy	1 month postpartum	6 months postpartum	1 year postpartum
Height	✓[a]	—[b]	—	—	—	—	—
Weight	✓	✓	✓	✓	✓	✓	✓
Percentage fat by BIA[c]	✓	✓	✓	✓	✓	✓	✓
Behavioral run-in	✓	—	—	—	—	—	—
Skinfold thickness	—	✓	✓	✓	✓	✓	✓
Waist and hip circumferences	—	✓	✓	✓	✓	✓	✓
Blood pressure	✓	✓	✓	✓	✓	✓	✓
Questionnaires	—	✓	—	✓	✓	✓	✓
Diet recall	—	✓	—	✓	—	✓	✓
Accelerometry	—	✓	—	✓	—	✓	✓
WIC[d] chart data abstraction	—	—	—	✓	—	—	✓
Birth certificate data abstraction	—	—	—	—	✓	—	—

[a]Assessment performed during this visit.

[b]Assessment not applicable or not performed during this visit.

[c]BIA: bioelectric impedance scale.

[d]WIC: women, infants, and children.

Maternal Outcomes and Measurements

Outcome assessments include a nonfasting measurement of height (screening visit only), weight, blood pressure (measured in duplicate after a 5-min rest), percent fat by bioelectrical impedance, skinfold thickness, hip and waist circumference, physical activity and sleep over 5 to 7 days using the Actigraph GTX3, dietary intake by 24-hour recall (National Institutes of Health, National Cancer Institute ASA-24), and evaluation of depression and anxiety (Depression Anxiety Stress Scales-21) [26], quality of life (Quality of Life Inventory) [27], household chaos (Household Chaos Questionnaire) [28], and infant feeding (Infant Feeding Styles Questionnaire) [29]. Upon delivery, the WIC chart and birth certificate are abstracted to provide data on prenatal, birth, and infant outcomes. To minimize missing data, home visits are permitted when a participant is unable to get to her WIC clinic (ie, bedrest).

Offspring Outcomes

The WIC chart of the infant will be abstracted to provide information on delivery outcomes (ie, adverse events, delivery complications, and route) and infant anthropometrics at birth. This will allow us to determine large or small for gestational age infants. As the mother will be followed until her infant's first birthday, the WIC chart will also have infant hemoglobin and weight and height measured at infancy and at 1 year.

Data Management and Analysis Plan

Data Storage

All data are entered into REDCap, a centralized data management system that allows for real-time, web-based data entry for community-based studies. Diet recall and Actigraph data are saved and stored on a centralized server that is only accessible to the study team.

Sample Size and Power Calculations

The sample size estimates assume β=0.8 and α=0.05 to detect the specified increases in the incidence rate of appropriate GWG. The sample estimate is inflated to allow 15% loss of data and maintain the desired power. The loss to follow-up accounts for participants who may drop out of the study and those who may be required to discontinue the intervention because of contraindications or safety alerts. A 15% discontinuation rate has previously been observed in our pregnancy trials [30]. The incidence rates of appropriate GWG for usual care were derived from women receiving WIC benefits in the 2013 Louisiana

Pregnancy Risk Assessment Monitoring System data. The estimated effect size for SmartMoms in WIC is based on our pilot trial data where the incidence of appropriate GWG for women with overweight was 12.3% for usual care versus 43.8% for SmartMoms; and for women with obesity was 0% for usual care and 42.9% for SmartMoms. However, as the pilot trial was not in an exclusive underserved population, we conservatively estimate that the Healthy Beginnings intervention will increase the incidence of appropriate GWG by a minimum of 14% across each BMI category. The resulting overall incidence rate would be similar to the observation in our previous trial [15].

In addition to the overall change in incidence rates, this study is also powered to detect BMI group changes in incidence rates. Assuming an overall average change in incidence rates of 14%, 122 participants in each BMI group (accounting for 15% attrition) are sufficient to detect an incidence rate that is at least 20% different between BMI groups.

We will also investigate the rate of GWG per week. According to the 2009 IOM guidelines, each BMI category is allocated a different rate of GWG per week [31]. We will investigate the deviation between the observed rates of GWG and rates deemed appropriate by the 2009 IOM. On the basis of our pilot data, women with overweight and obesity in the SmartMoms group had similar deviation rates (gaining an additional 0.06 kg per week above the recommended amount), whereas the usual care group had a much higher rate of weekly GWG. With our planned sample size of 432 participants, we have >80% power to detect changes as small as 0.12 kg per week between the Healthy Beginnings intervention and usual care and within each BMI category, and >99% power to show overall differences in rates of weekly GWG.

Analytical Plan

Statistical analyses will be completed using SAS/STAT software, version 9.4, of the SAS System for Windows by a PhD-level biostatistician. All tests will be performed with significance level α=.05 and using an intent-to-treat analysis. Outcomes will be assessed for normality (where appropriate) using the Shapiro-Wilk test. If transformed data are still not normally distributed, then nonparametric analyses will be conducted on these outcomes. Least-angle regression (LARS) will be used for the covariate selection methodology. Covariates will include, but may not be limited to, the infant's sex, gestational age at delivery as well as and the maternal age, weight at screening, parity, race or ethnicity, and gestational diabetes status. Treatment and BMI categories will be included in all models. Intent-to-treat analysis will be the primary analysis type. Both completers and multiple imputation (Markov chain Monte Carlo method, preferred) may also be performed if there is a large amount (>10%) of missing data. However, we will extract the mothers' WIC record and therefore for participants who fail to return to the clinic, weight measurements will be acquired from the planned chart abstraction. This should greatly decrease the amount of missing data from loss to follow-up.

For the incidence rate of appropriate GWG, initial results will be expressed contingency tables with incidence rates and either treatment or BMI category. Tests for associations between these variables will be based on the Pearson chi-squared statistic. Further results will be based on a generalized linear mixed effect model with a binary distribution and a log odd link function modeling the incidence rates. The model will use random effects to account for a site effect and within-subject correlation over time. Results from this model will be reported as odds ratios of least square means, with *P* values based on z tests. Two different sets of models will be used. The first set of models will contain only treatment and BMI categories, whereas the second will also contain the covariates based on LARS. Pairwise post hoc comparisons of the category variables will be corrected for multiple comparisons when necessary.

For the key secondary outcome of weekly GWG rate, overall deviation rates will be reported using a linear effect mixed model, using random effects to account for site and within-subject correlation. The response is the deviation of the weekly GWG rates from the IOM guideline rates. Models will be reported using both the simple model with treatment and BMI categories and with the covariates selected by LARS. Adjusted means of the deviations will be obtained using the least squares means. A two-sample *t* test will be used to compare adjusted mean deviations. For other secondary outcomes, each physiological and behavioral factor will be investigated independently from each other. Linear mixed effect models will be used to test differences between the treatment groups with least square means. The response for each of these models will include both repeated measures and percent change from baseline approaches.

Results

Phase 1 of this trial was completed in July 2019. The delivered outcomes of phase 1 are the produced Healthy Beginnings intervention curriculum, including development of the gamification component of the intervention and adaptability of the intervention to ensure cultural sensitivities and an appropriate level of health literacy. The produced Healthy Beginnings intervention curriculum is being used in the randomized controlled trial in phase 2. The randomized controlled trial is ongoing, and all data are anticipated to be collected by spring 2023. The final sample of 432 enrolled women is expected to be diverse in BMI and geographic region.

Discussion

With the recent identification that pregnancy may program the future health of mothers and babies, there has been heightened interest in developing programs in pregnancy that foster appropriate GWG. There is a growing list of trials showing that behavioral interventions focused on diet and physical activity modification can reduce excess GWG in pregnant women [15,32-34]. The next phase of research calls for the translation of effective approaches to community-based programs with the overarching goal to offer more widespread benefit to mothers and their children. Implementation research requires consumer and stakeholder engagement not only to ensure effective translation of the program into the community but also in the design of pragmatic trials in which the community-based eHealth program can be properly evaluated.

The SmartMoms in WIC project is unique in that it is a biphasic clinical trial. First, phase 1 of the project utilizes a formative research model to incorporate feedback from key stakeholder groups in the adaptation of the intervention for economically disadvantaged pregnant women and development of the new curriculum with increased specificity. Second, the newly adapted eHealth behavioral intervention, Healthy Beginnings, is studied in a pragmatic, state-wide randomized controlled trial to test its effect on increasing the incidence of appropriate GWG for women enrolled in WIC across Louisiana.

In our pilot trial, we demonstrated that our SmartMoms intervention was more cost-effective than the same intervention delivered in person. Thus, successful implementation of the new Healthy Beginnings intervention would provide a scalable, personalized, and cost-effective intervention to promote adequate GWG and ultimately to minimize adverse pregnancy, infant, and postpartum outcomes. It is estimated that 77% of adults in the United States own a smartphone [35], and in low-income households, families are more likely to rely solely on mobile devices for internet access [36]. With smartphones, individuals are *mobile* and less reliant on computers for internet access. Furthermore, many insurance programs offer smartphones for pregnant women throughout their pregnancy. The WIC program already offers several smartphone apps [37], and WIC could choose to adopt this intervention framework for use by their pregnant clients. Therefore, if the Healthy Beginnings intervention proves effective in increasing the rates of healthy GWG, the packaging of health information via a smartphone app available to all pregnant women utilizing WIC services makes widespread implementation and distribution feasible and with little burden from WIC staff, which is commonly acknowledged as a roadblock for the implementation of longstanding programs. Furthermore, as the intervention is delivered remotely, the Healthy Beginnings intervention is scalable and has the potential to reach WIC clinics beyond the state of Louisiana.

SmartMoms in WIC has several strengths that distinguish the trial and promote an advance in the field. First, formative research to adapt the curriculum for the target population through 2 independent community advisory groups ensures that health information is relevant and engaging when maintaining value systems and cultural beliefs. Second, the trial is being conducted statewide and aims to evenly enroll women across the 9 regions of the Louisiana Department of Health. This distribution avoids confounding effects of geographical location or WIC clinic staff influence. Third, near real-time participant feedback from the smartphone allows for immediate participant engagement in weight and physical activity levels, which allows participants to make necessary behavior changes independently. However, if corrections are not met, intervention staff will coach the participant through difficulties, providing added support to assist in meeting weight gain goals. Flexibility in participant clinic visits provides the greatest chance of success in obtaining primary outcome measures. If participants move outside the area within the study timeframe but remain within the state of Louisiana, study outcomes can be obtained at the participant's new WIC clinic. Understanding that transportation is often a barrier for low-income women to attend clinic visits, home visitation is permitted by clinic assessment researchers if a participant's transportation situation changes throughout the study timeframe. Finally, as smartphone use is already highly prevalent in low-income populations, eHealth interventions can overturn many of the reported barriers for intervention adherence and completion.

Although the Healthy Beginnings intervention is designed with widespread implementation in mind, the current randomized controlled trial does not yet test implementation and integration of the program into WIC. Although the partnership with WIC is an essential component for trial success, it is important to recognize that the trial is led by an experienced research team independent of WIC. Therefore, if the study demonstrates the effectiveness of the intervention for increasing compliance with the IOM recommendations for weight gain in pregnancy, the next step will be to test implementation within the WIC clinics. A limitation of pragmatic trials involving community stakeholders is the possible disconnect between the stakeholder groups and funding bodies. For example, the WIC Mothers' Advisory Group requested that the outcomes of the trial include health markers other than simply weight gain (eg, glucose and lipids obtained through capillary blood). The mothers explained that understanding the full health benefit of adhering to a lifestyle program in pregnancy would be more informative for their future participation. Interestingly, the scientific review panel was less enthusiastic about including such measures. It is important to note that there may be a disconnect between the crosstalk of community stakeholders and scientific reviewers in the value of additional health information, which can pose a challenge when executing community-based research.

Conclusions

The status of maternal health during pregnancy has lifelong consequences for women and children and is therefore a public health problem. Furthermore, inappropriate weight gain in pregnancy is a significant health issue, particularly in low-income women, increasing the probability of adverse pregnancy outcomes. The original SmartMoms curriculum was methodically adapted using feedback from community-based peer advisory groups to create a culturally relevant mobile behavioral intervention. The new Healthy Beginnings intervention promotes healthy eating behaviors and physical activity patterns in economically disadvantaged pregnant women through education, immediate participant feedback, and coaching from trained intervention staff. If Healthy Beginnings is efficacious when embedded in the Louisiana WIC program, it will provide the first indication that WIC services could be efficiently expanded to meet an important public health need and serve as a conduit for delivering an eHealth intervention to pregnant women across the country. Furthermore, given the long-term follow-up of children in the WIC program, this study also provides a framework for future investigations into the effects of pregnancy interventions on health outcomes in children.

Conflicts of Interest

LR, the principal investigator of this research study, is also a coinventor of the SmartMoms technology. LR does not currently have any financial gain from SmartMoms; however, it is currently available for licensing through LSU-Pennington. If a license is acquired, LR may possibly receive a royalty payment. All other authors have no conflicts of interest to declare.

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Abbreviations

DBP: diastolic blood pressure
GWG: gestational weight gain
IOM: Institute of Medicine
LA CaTS: Louisiana Clinical and Translational Sciences Center
LARS: least-angle regression
PBRC: Pennington Biomedical Research Center
SBP: systolic blood pressure
WIC: women, infants, and children

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Protocol

Awareness of and Attitudes Toward User Involvement in Research on Aging and Health: Protocol for a Quantitative Large-Scale Panel Study

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Abstract

Background: User involvement is a requirement of most research funders. There is a growing body of literature exploring the benefits and challenges of user involvement in research, but such studies are scarce in the field of aging and health. Moreover, the majority of such research is qualitative, which limits the generalizability of results. The UserAge panel study will be instrumental in expanding knowledge that will benefit the quality and impact of user involvement in future research.

Objective: The aim of this study is to determine the awareness and understanding of and attitudes toward user involvement in research among different categories of knowledge users and researchers over time.

Methods: A panel study will be implemented with 3 different categories of knowledge users (people aged 60 years and older, informal carers, and professionals in health care and architecture) and researchers in aging and health. A professional survey company will collect data from all samples in parallel. Potential participants will be asked to complete the survey via telephone or online, or participants can request a paper survey to be sent to them in the post. A draft set of questions on attitudes and behavioral patterns related to research utilization and user involvement in research was compiled based on existing literature and input from the research team. Using a participatory approach, we engaged a user forum, where 8 older people and 3 researchers jointly refined the survey for time/length to complete, terminology, readability, and context. Data collected via the internet or telephone will be automatically processed, and data collected on paper forms will be entered in machine-readable forms. The survey company will store all data and deliver the quality-controlled database to the university for further storage. Analyses of frequencies and measures of central tendency will be used for descriptive purposes. To compare groups, state-of-the art statistical analyses will be used.

Results: Data collection for the first study wave started in September 2019 and will be completed in spring 2020. Data will be ready for analysis following cleaning and quality control, which started during summer 2020 and will be completed autumn 2020. We anticipate the data collection for the second study wave to start in September 2021.

Conclusions: This is the first quantitative large-scale panel study focusing on trends in attitudes toward, awareness of, and knowledge about user involvement in research on aging and health in Sweden. The results will generate new and important knowledge to advance the understanding of user needs and preferences as well as the relevance of user involvement in research on aging and health.

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KEYWORDS

partnerships; public involvement; older people; UserAge program; user participation

Introduction

Background

The rising proportion of older people in the population has increased the demand for new solutions and targeted public and welfare services. Among these are aging-related policies addressing infrastructure, health care, social services, and housing [1]. In order to develop efficient strategies and ensure that research on aging and health is effectively translated and promptly put into practice, policy makers underscore the need to involve different categories of knowledge users in the research process [2,3]. Although patient and public involvement is increasing in fields such as mental health and disability [4-6], aging and health research is lagging behind. There is limited knowledge about the awareness of and attitudes toward user involvement among aging and health researchers and the different categories of knowledge users who could be involved. Such studies have typically involved representatives of nongovernmental, senior citizen, and patient organizations. Older people are a heterogeneous group with diverse preferences and needs. They want the opportunity to influence the products and services they need and would like to choose from a variety of options, but little is known on the opinions about user involvement in research on aging and health in the general population of older adults.

According to the World Health Organization (WHO) [7], "knowledge users" represent all those who are interested in or able to directly or indirectly benefit from aging and health research results. For example, knowledge users may include older people in the general population or those with specific needs; informal carers; patients; health care, social services, and industry professionals; and public agency, policy makers, and interest organization representatives. Knowledge users are those in a position to identify problems and act on research recommendations [8]. User involvement in this context is seen as *active* involvement of knowledge users as partners in any stage of the research process and not as research subjects or study participants in the traditional sense [9]. Hence, user involvement in this study protocol paper refers to research that is conducted "*with* or *by*" knowledge users rather than "*to, about,* or *for*" them [9]. User involvement may help researchers to understand some of the complex and context-specific nature of health and social problems experienced by older people [10] as well as practice and policy change [9], and contribute to the development of age-friendly services and communities [11]. Yet, such studies are few, and we know very little about how different categories of knowledge users and researchers perceive user involvement as a phenomenon in this field of research.

Systematic literature reviews have reported many ways in which user involvement impacts research processes and outcomes as well as the people involved [12-14], but the evidence has been criticized as being weak and unreliable [15]. A main reason for this criticism is that research on user involvement, so far, has been dominated by small-scale qualitative studies [16,17]. This limits the generalizability of results, and the accumulation and building of knowledge for the future is slow. Although qualitative studies are highly commendable to gain in-depth knowledge, quantitative studies are necessary to establish a broad knowledge base that can be used to make inferences about relevant populations.

Research on attitudes toward user involvement has primarily focused on patients and clinicians [18] rather than the general population, including societal sectors other than health care and social services and researchers. Because the ongoing demographic shifts extend the demands on the delivery of welfare services, broader and additional categories of knowledge users such as representatives from the complex field of housing construction and provision need to be involved in research partnerships [19,20].

Qualitative research with a small number of participants reveals that health researchers recognize the potential benefits of user involvement, but the procedures are challenging [21]; researchers as well as knowledge users have highlighted the need for more training in this area [22]. Moreover, concerns have been raised about the strong political imperative to involve knowledge users, which may cause problems if researchers do so out of necessity rather than thoughtful commitment [23]. Thus, systematic approaches based on state-of-the-art methodology are needed to address these issues in a manner that generates reliable and valid results.

Involving knowledge users actively in the research process is a complex and context-dependent exercise [24]. A more thorough exploration of attitudes toward user involvement from both knowledge users' and aging and health researchers' points of view can help to create more favorable conditions for such studies to succeed. Furthermore, solid and reliable evidence is needed to determine which categories of knowledge users should and could be involved in research on aging and health. Expanding such knowledge will promote research partnerships as well as inform policy makers and funding agencies about how to increase the quality and impact of user involvement in research on aging and health. The UserAge panel study will be instrumental in this vital knowledge quest.

UserAge and the Panel Study

UserAge is a 6-year research program designed to expand the understanding of user involvement in research on aging and health [25], with the integration of researchers and different categories of knowledge users at the core. The program is implemented as a national 4-university endeavor with international collaboration. Currently, 19 researchers and 4 PhD students representing different disciplines and research fields (eg, cognitive science, design sciences, gerontology, health sciences, philosophy, psychology, and sociology) are engaged in the program. UserAge is based on previous and ongoing research with various forms of participation involving different categories of knowledge users (eg, people in the general aging population; older people with frailty; older migrants; older people with substance abuse problems; informal carers; interest organization representatives; health care, social services, construction sector, transportation sector, and tech sector professionals; research institutes; public agency officials; and policy makers). The aim of the UserAge program is to enhance the execution of high-quality research and to increase the knowledge about the added value stemming from user

involvement in the research process. The panel study described in this protocol paper is one of the empirical projects of the program.

The panel study has 2 primary aims addressed toward different categories of knowledge users and researchers in aging and health in Sweden:

1. What are the awareness and understanding of and attitudes toward user involvement in research?
2. Are the awareness and understanding of and attitudes toward user involvement in research changing over time?

Methods

In collaboration with the program's User Board, we established a user forum with 8 members representing older people, 2 researchers (authors MK and OJ), and 1 doctoral student. The user forum provided input into the final methods used for recruitment, procedures for data collection as well as content for the questionnaire.

Study Design

The study design is a panel study with a baseline survey and at least 1 follow-up survey. With a longitudinal design such as a panel study [26], trends in attitudes toward and awareness and knowledge about user involvement in research on aging and health will be elicited over time. Panel studies also allow for replacement of participants when lost at follow-up. Collecting data at different points in time has the advantage of revealing shifting attitudes and patterns of behavior [27] that might go unnoticed with other research designs.

The baseline data collection period is autumn 2019 to spring 2020. The first follow-up will take place in 2021-2022; pending additional funding, a second follow-up is planned 2 years thereafter, that is, 2023-2024. Based on the results of the baseline survey and findings from other projects within the UserAge program [25], the survey questionnaires and data collection procedures will be refined. While all core questions will be used repeatedly, a few items might be added or slightly modified.

Participants and Recruitment Strategy

The targeted study sample sizes for the different categories of knowledge users and researchers (in total, N=1500, see Table 1) are as follows:

1. People aged 60 years and older (60+ sample, n=1200)
2. Informal caregivers (carers sample, n=100)
3. Professionals within health care and architecture (professionals sample, n=100)
4. Researchers in aging and health (researcher sample, n=100)

Table 1. Overview of study samples, inclusion criteria, recruitment, and data collection methods.

Methods	Panel study samples (N=1500)			
	60+	Carers	Professionals	Researcher
Sample size, n	1200	100	100	100
Participants	People from the general population	Informal carers	Professionals	Researchers within aging and health
Inclusion criteria	Aged 60 years or older	Aged 60 years or older, or caring for someone who is 60 years or older	Professionals within health care or architecture, with relevance for aging and health	Experience of research on aging and health
Recruitment strategy	Random sample selected from national population registry data, stratified by sex	Convenience sample recruited from the organization Carers Sweden	Convenience sample recruited from a memory clinic (health care professionals) and advertisement in a professional newsletter (architects)	Convenience sample recruited from partner universities affiliated to the Swedish National Graduate School for Competitive Science on Ageing and Health and the Swedish Gerontological Association
Data collection method	• Web-based survey • Telephone survey • Postal survey	• Web-based survey • Telephone survey • Postal survey	Web-based survey	Web-based survey

The age range for inclusion (60 years and older) was set in consensus discussions among members of the user forum. Representatives of older people proposed this relatively low age with arguments that it takes time to contribute to societal change in many aging- and health-related issues, such as preventative work and housing for later life. The researchers saw potential benefits to include not only today's but also tomorrow's senior citizens. With the 60+ group, we are striving for a representative sample, with participants randomly selected from the Swedish national population registry, stratified by sex. Based on population data from Statistics Sweden (2017), there are approximately 2.57 million (52.8% women) people aged 60 years and older. Using a confidence level of 95% and a margin of error of 4, we estimate a total sample size of 1200 (600 women and 600 men) to be nationally representative [28]. Based on recent experiences with surveys in Sweden targeting older people [29], we expect a 50%-60% response rate. Thus, we will draw an initial random sample of N=2400. Using established techniques to substitute for dropouts over time [30], the goal is to maintain the sample size for the 60+ sample longitudinally. Additionally, during recruitment of wave 2, to achieve a representative sample, we will oversample those groups of the

population who were under represented during wave 1. Recruitment will continue until the targeted number of participants within each stratum complete the survey.

The carers sample (n=100) will be a convenience sample of informal carers recruited from Carers Sweden's (a non-governmental organization that supports carers, independent of any political or religious affinity) member list. In this study, informal care refers to unpaid care provided by significant others such as family, close relatives, or neighbors. Anticipating a 33 % response rate based on previous experiences, carers Sweden will post invitations to 400 of their members. Only carers aged 60 years or above or caring for someone who is 60 years or older will be included. Recruitment will continue until 100 informal carers have responded.

The professionals sample (n=100) will be a convenience sample. One sample will be health care professionals from a university hospital memory clinic, which has primarily older patients with various symptoms of cognitive decline such as dementia. The operations manager for the memory clinic will send out an invitation to the survey to employees, which includes nurses, occupational therapists, physiotherapists, and medical doctors. The other sample will be architects, interior architects, landscape architects, and spatial planners recruited from a professional organization with 13,000 members. We will advertise the survey once in their weekly newsletter. Recruitment for the professionals sample will continue until 100 professionals have responded.

The Researcher sample (n=100) will be recruited through the national partner networks of the Swedish National Graduate School for Competitive Science on Ageing and Health (SWEAH) and the Swedish Gerontological Society (SGS). An invitation will be emailed to members/affiliates of both organizations. Recruitment will continue until 100 researchers have responded.

Procedure

A professional survey company (Kantar Sifo) with longstanding expertise will implement the data collection. Each sample will receive an invitation letter that describes the project and information about the participants' role and rights if they choose to participate. The invitation letter and survey for study samples 1-3 are in Swedish, while the survey for the Researcher Sample is in English. Samples 1-3 will receive information about the opportunity to sign up for interest to get involved in other parts of the UserAge Program (eg, engage in user fora to discuss and test research ideas, methodologies, evolving results, and practical solutions with researchers; participate in qualitative studies on user involvement in research). Instructions describe how to complete the survey via telephone, at an online secure web-page, or through a postal survey, as well as how to decline participation. The professionals and the researchers sample participants will only be able to respond to the survey online. Approximately 2 weeks after the letters are posted, trained interviewers from the survey company will call potential participants who have not completed the survey online or have not declined participation. Once telephoned, potential participants can choose one of the following options:

1. Request to be called at a different time/date to complete the survey
2. Request to complete the survey online
3. Request a paper version of the survey be sent to them in the post
4. Complete the survey immediately via telephone
5. Decline to participate

Data collection for all samples will be conducted in parallel. For potential participants who decline to participate, the survey company will ask them an open-ended question about why they have declined. This information will be used to identify risks to the representativeness of the 60+ sample.

Panel Study Questionnaires

As a first step in an iterative process, the research team developed a draft set of questions on attitudes and behavioral patterns related to research utilization and user involvement in research on aging and health. Questions were based on existing relevant instruments [31-33] and iterative input from core researchers in UserAge. The user forum was engaged to jointly refine the survey for content, time/length to complete, readability, tone-of-voice, and understandability and to put questions into context. Members of the user forum provided input on the development of the invitation letter and method of survey implementation (phone, paper, and web). The user forum involved three 3-hour sessions during a 2-month period. Furthermore, a web seminar with UserAge researchers provided additional input, resulting in a core set of questions for the 60+ sample (see Table 2 for examples of questions included in the survey). The survey for the carers sample and professionals sample is based on the same core questions but modified to fit the perspective of the respective category of knowledge users. The survey for the Researcher Sample was compiled based on existing literature and feedback from UserAge researchers, as well as a set of comparable core questions. All 4 surveys included demographic questions such as age, sex, and level of education. In addition, the surveys for samples 1-2 included questions on perceived health and functioning. Prior to the data collection, a pilot study will be completed for the 60+ sample (n=25), carers sample (n=15), and researcher sample (n=15). Following this, the number of invitations to reach the targeted study sample sizes and questions may be slightly modified. As we intend to limit the time burden on participants to a maximum of a 10- to 15-minute phone survey, items may be removed from the survey based on the pilot study experiences and findings.

Table 2. Key sections and exemplar questions and responses translated to English.

Section and examples of questions in the survey	Response alternatives and scales
Awareness and understanding	
Do you know that you can participate actively in the actual conduct of research? For example, give comments on questionnaires, membership in user boards, help to recruit study participants, or disseminate research results.	Yes/No/Don't know
How interested are you in research on aging and health?	5 response alternatives ranging from "not at all" to "very much"
Would you consider actively participating in research on aging and health?	Yes/No/Maybe
If you had the opportunity, how likely is it that you would want to participate by... • Contributing to the planning and design of research projects. • Being part of a user board, reference group, user panel or similar. • Carrying out tasks in research projects. • Analyzing the data produced. • Disseminating research results. • Contributing to an application for research funding.	5 response alternatives ranging from "not at all" to "very much"
Attitudes	
People who are affected by research have a right to have input on what and how research is undertaken.	4 response alternatives ranging from "strongly disagree" to "strongly agree"
Due to the fact that users[a] in general have valuable life experiences, they should be actively involved in research on aging and health.	4 response alternatives ranging from "strongly disagree" to "strongly agree"
User involvement is a symbolic political initiative that has questionable value for the results.	4 response alternatives ranging from "strongly disagree" to "strongly agree"
Users[a] should be actively involved in any publicly funded research on aging and health.	4 response alternatives ranging from "strongly disagree" to "strongly agree"
Facilitators and barriers	
Through which channels do you prefer to be informed about opportunities to participate actively in research on aging and health?	Checkbox and free-text options. Letter in post, advertisement or article in newspaper, internet/social media, personal phone call, email, SMS, TV/radio, public meeting/conference or lecture, advertisement on message board, or other (specify).
What could motivate you to participate actively in research on aging and health?	Checkbox and free-text option. Getting priority to services (eg, health care, social care, services, housing); to feel important; to find out more about my situation; to contribute to society; you have nothing to lose; research should go forward; to connect with others in the same situation; being helpful to the researcher; getting better services; finding out what the study will lead to; the research is about something that you think is important; others (specify); or nothing, you do not want to be actively involved in research.

[a]Instead of the term "user," Swedish terms defining the targeted category were used in samples 1-3: "private individuals" in the 60+ sample; "carers" in the carers sample; and "professionals" in the professionals sample.

Quality Control and Data Handling

At the start of the data collection, a researcher (MK or OJ) will monitor 25 of the first 100 telephone surveys to ensure procedures are followed for data quality. Throughout the data collection, periodic spot checks of the telephone surveys will be conducted to ensure that the telephone interviews are administrated in accordance with the agreed procedures. In total, 5 % of all telephone interviews will be listened to, simultaneously in real time, by 1 of the researchers (OJ). Furthermore, after 10% of the surveys are completed, a data quality check will be conducted by the survey company to identify any systematic errors in the data collection or data entry process. Data collected via the internet or telephone will be automatically processed, and paper surveys will be entered in machine-readable forms. All data will be stored by the survey company in a secure database in compliance with The General Data Protection Regulations (GDPR). The survey company will conduct a manual quality control check on all paper surveys.

Upon completion of the data collection and quality control, the survey company will develop a set of weights (numerical coefficients) for the cases to adjust for any underrepresented segments of the population in the 60+ sample to ensure representativeness. The following key characteristics will be considered: sex (male/female), age (60/65-65/70-70/75-80/85+ years), and geographic regions. People with underrepresented

characteristics will be given higher weights, if necessary, while overrepresented characteristics will be restrained.

The complete data file will be encrypted by the survey company and transferred to the researchers and stored on Lund University's platform for storing, handling, and analyzing data in a high-secure way (LUSEC). Only project researchers will be able to access the data within LUSEC. All analyses will be conducted using statistical software available within this platform (eg, SPSS and STATA).

Data Analysis

Frequencies and measures of central tendency will be used for descriptive purposes. Exploratory comparisons between the groups will be used to identify differences in awareness of, understanding of, and attitudes toward user involvement in research. To compare groups, appropriate analyses will be selected based on the type of data (ie, ordinal, nominal, and continuous). Although no power calculation was conducted for comparisons across samples, as most of the survey items are categorical (yes/no) or ordinal (4 or 5 levels), we estimated that the selected sample sizes would provide adequate cell sizes for analyses. Specific data analyses will be reported in the methods sections of future publications. When applicable, we will use statistical methods such as multivariate regression and methods to deal with repeated measurements. In all analyses, two-sided *P* values will be used at a significance level of .05.

Ethics

Ethical approval has been obtained from the Ethical Board in Lund (No. 2018/986; Dec 2018). Participation in the study should not present any significant risks, as the questions are not expected to elicit any sensitive or emotional reactions from participants. Participation is voluntary and participants can withdraw from the study at any time.

The survey company staff are specialized in conducting telephone surveys and will undergo project-specific training. We will ensure that they repeat the purpose of the study prior to each survey, speak in a clear and polite manner, and give potential participants an additional opportunity to decline to participate. The participant's right to discontinue the survey at any time will be clearly stated. The survey company staff will explain that all data will be handled in accordance with GDPR standards, protecting unauthorized access. It will be clearly explained on the paper version, by the telephone interviewer, and on the web-based survey that completion of the survey constitutes informed consent to participate in the study.

Availability of Data and Material

The datasets generated and analyzed during this study are not publicly available due to a data use agreement between Lund University and Kantar Sifo but are available from the corresponding author on reasonable request.

Results

Funding for the larger UserAge program started in January 2017 and will continue for 6 years. The data collection for the first study wave started in September 2019 and will be completed in spring 2020. Data will be ready for analysis following cleaning and quality control, which started during summer 2020 and will be completed autumn 2020. As of submission of this protocol, we have enrolled the following samples:

1. n=881 in the 60+ sample. Based on lessons learned from the pilot study, the random sample was increased to N=3000
2. n=150 from the carers sample after additional referral sampling
3. n=65 from the researcher sample
4. n=11 from the professionals sample

We anticipate the data collection for the second study wave to start in September 2021.

Discussion

This paper provides a detailed description of a panel study, which is a part of the 6-year UserAge Program [25]. The panel study addresses key questions about the awareness and understanding of and attitudes toward user involvement in research among different categories of knowledge users and researchers. Given that research about and with user involvement is dominated by qualitative approaches [24], our study makes a valuable contribution by generating quantitative data that can be used to make inferences about relevant populations. In order to create favorable conditions for future research, it is crucial for aging and health researchers to understand the awareness and understanding of and attitudes toward user involvement among older people and informal carers. Importantly, by including 3 different categories of knowledge users as well as aging and health researchers, the panel study will generate new knowledge about how different categories of knowledge users perceive user involvement as a phenomenon in a research area of high societal relevance.

Involving different categories of knowledge users, each with specific needs and prerequisites, in research comes with specific challenges [34] hitherto insufficiently explored and addressed in a rigorous manner. In the panel study, the 60+ sample and the carers sample can choose to complete the survey via telephone, an online web page, or a postal survey. This approach will give more people the possibility to participate in the study [35], that is, if they do not have access to the internet or are unable to fill out a paper survey themselves, the telephone survey might be a favorable alternative. We will learn important lessons to optimize forthcoming data collection waves.

Methodological issues are of significant importance [14] because research funders today often ask for user involvement in their calls for research proposals. Accordingly, it is important to enhance the knowledge about the challenges of involving knowledge users in research on aging and health and about how to best handle them. Based on the overall goals of the UserAge program, of which the panel study is one of the numerous empirical studies, the intention was to include professional groups represented in different parts of the program. We thoroughly discussed different strategies to recruit participants representing health care and social services as well as housing and planning sector professionals. However, we experienced substantial challenges in this recruitment process and ended up with a less optimal sample in the first wave of data collection.

A limitation worth mentioning in this context is that for the professionals sample, researcher sample, and carers sample, we used convenience sampling. In Sweden, there is no national registry or other means to identify the members of these 3 populations to randomly sample. Although we could have attempted to sample from the member lists of different professional or labor organizations in the health care, social services, and construction sectors, we did not have the resources necessary to do so in a valid manner. Thus, this part of the panel study mainly served as an exercise to gain experiences for future data collection waves, and the sample sizes attained in the first wave suggest a need to reconsider the sampling strategy. Another noteworthy challenge is the difficulties to clearly identify the target populations (professionals, researchers, and carers), which partly explains why we did not calculate statistical power; accordingly, these results cannot be extrapolated beyond the respondents. With lessons learned about recruitment and response rates, we will be in a stronger position to raise the level of ambition for forthcoming data collection waves. Nevertheless, our approach to include different categories of knowledge users, including participants without experiences of user involvement, in a large-scale panel study focusing on trends in attitudes and knowledge about user involvement in research on aging and health in Sweden has not previously been applied.

In conclusion, to the best of our knowledge, very few—if any—results from larger studies exploring attitudes and experiences of user involvement in research among the general population of older adults have been reported. As such, the UserAge panel study will provide results that can be used to inform research funders and policy makers about the prerequisites needed to efficiently conduct research with user involvement. This can lead to more relevant findings to improve well-being in later life; improve the ability of research partnerships to benefit from diverse knowledge users' local, lived, or applied knowledge; and jointly address the challenges of the aging society in the best possible way. Findings from the panel study may create conditions to improve approaches to involve knowledge users (eg, channels for recruitment, meet interests and expectations, handle barriers) to increase the quality and impact of research as well as give knowledge users participating in research a meaningful experience. In addition, knowledge derived from the panel study will contribute to the development of reliable and valid methodologies to evaluate research with user involvement.

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Authors' Contributions

SI and SMS conceptualized the study; all the authors have contributed to the panel study survey methodology. SI and SMS drafted the grant application with contributions from BS and OJ. MK wrote the ethical application together with SMS and BS, with input from SI and OJ. MK led the writing of this study protocol manuscript. All the authors have been involved in revising it critically and have approved the final version.

Conflicts of Interest

None declared.

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Abbreviations

GDPR: General Data Protection Regulations
SGS: Swedish Gerontological Society
SWEAH: Swedish National Graduate School for Competitive Science on Ageing and Health
WHO: World Health Organization

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Corrigenda and Addenda

Correction: Nurse-Delivered Cognitive Behavioral Therapy for Adherence and Depression Among People Living With HIV (the Ziphamandla Study): Protocol for a Randomized Controlled Trial

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In “Nurse-Delivered Cognitive Behavioral Therapy for Adherence and Depression Among People Living With HIV (the Ziphamandla Study): Protocol for a Randomized Controlled Trial” (JMIR Res Protoc 2020;9(2):e14200) the authors noted one error.

Under the Methods section subheading "Secondary Outcomes: HIV Viral Load and CD4 Cell Count," the lower limit of the range of detection for the COBAS AmpliPrep/TaqMan HIV-1 test was reported incorrectly as 48. The actual lower limit of this test is 20. The original text reporting this value read:

> *Participants who do not have viral load test results within 1 month of the baseline assessment or 4-, 8-, and 12-month follow-up undergo a blood draw for assay using the COBAS AmpliPrep/TaqMan HIV-1 test (range: 48-10,000,000 copies/mL) [50].*

This sentence has been corrected to read:

> *Participants who do not have viral load test results within 1 month of the baseline assessment or 4-, 8-, and 12-month follow-up undergo a blood draw for assay using the COBAS AmpliPrep/TaqMan HIV-1 test (range: 20-10,000,000 copies/mL) [50].*

This change does not affect the overall findings of the paper.

The correction will appear in the online version of the paper on the JMIR Publications website on September 28, 2020, 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

The Impact of Brexit on the Pharmaceutical Supply Chain of the United Kingdom: Scoping Review Protocol

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Abstract

Background: The continuing uncertainty around Brexit has caused concern in the pharmaceutical industry and among health care professionals and patients. The exact consequences of Brexit on the pharmaceutical supply chain in the United Kingdom will depend on whether a deal is reached and what it entails, but it is likely to be affected by the withdrawal of the United Kingdom from the European Union. Regulatory issues and delays in supply have the potential to negatively affect the ability of UK residents to receive an adequate and timely supply of necessary medicines.

Objective: The purpose of this protocol is to provide an overview and critical analysis of current perspectives on the effect of Brexit on the UK pharmaceutical supply chain.

Methods: The PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) guidelines will be used to structure this protocol. A systematic search of MEDLINE, EMBASE, PsycINFO, Healthcare Management Information Consortium (HMIC), Cochrane, Web of Science, Business Source Complete, EconLit, and Economist Intelligence Unit will be conducted, as well as a Google and Nexis.UK search for grey literature such as reports, opinion pieces, and press releases. Two reviewers will independently screen the titles and abstracts of identified references and select studies according to the eligibility criteria. Any discrepancies will then be discussed and resolved. One reviewer will extract data from the included studies into a standardized form, which will be validated by a second reviewer. Risk of bias will be assessed using the Cochrane Collaboration Risk of Bias tool for any randomized controlled trials; quality will be assessed using the relevant Critical Appraisal Skills Programme (CASP) checklists; and grey literature will be assessed using the Authority, Accuracy, Coverage, Objectivity, Date, Significance (AACODS) checklist. Outcomes include the agreement between sources on the potential, likelihood, and severity of the consequences of Brexit on the UK pharmaceutical supply chain.

Results: Results will be included in the scoping review, which will be published in 2020.

Conclusions: This scoping review will summarize the currently expected consequences of Brexit on the UK pharmaceutical supply chain.

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KEYWORDS

Brexit; drug industry; pharmaceutical supply

Introduction

The long uncertainty around whether and how the United Kingdom will leave the European Union ("Brexit") makes it difficult to predict the exact consequences for the health care system at the time of writing (December 31, 2019). These consequences will depend on what trade deals are arranged between the United Kingdom and European Union (EU), how involved the United Kingdom will remain in EU health care systems, the transition time allowed for companies to adapt to new regulations, and which EU regulations will be adopted into British law [1]. No matter the exact conditions of Brexit, however, changes to the relationship between the United Kingdom and EU are likely to have implications for the authorization and accessibility of medicines [2]. The uncertainty around how Brexit will occur has already caused concern in the pharmaceutical industry and preparation for a worst-case scenario [3]. In 2017, pharmacists were already reporting that this restructuring of the supply chain was causing medicine shortages [4].

The pharmaceutical supply chain is likely to be affected by Brexit at numerous stages. The United Kingdom is currently a member of the European Medicines Agency (EMA), which facilitates the single market for medicines in the EU [5]. If the United Kingdom leaves with a deal, there will be an important transition period that should prevent large disruptions of medicine supplies [4]. If there is no deal, the United Kingdom will immediately not be subject to EU law or EMA regulations, which could affect supply [5]. The extent of United Kingdom involvement in EU pharmaceutical activities will affect drug production, authorization, regulation, trade, health and safety monitoring, and research [3,4,6].

Depending on the post-Brexit UK-EU relationship, pharmaceutical companies might need separate centers in the United Kingdom and EU to test and release medicines, which could incentivize moving their headquarters from the United Kingdom to the EU, as the EMA already did [3,6]. The EMA currently approves marketing authorizations for the entire EU, but if the UK Medicines and Health products Regulatory Agency (MHRA) is unwilling to accept EMA decisions, drugs will need to undergo an additional authorization process to reach UK markets [7]. This will likely mean increased costs and delays in medicines becoming available in the United Kingdom and could deter companies from selling their medicines in the UK market altogether [3,4,6]. Additionally, if the United Kingdom is unwilling to accept regulatory requirements from other agencies, such as the EMA or the Food and Drugs Administration (FDA) of the United States, a new regulatory system will need to be developed [6].

If the United Kingdom leaves the EU without a deal, World Trade Organization (WTO) rules will come into effect [8], and tariffs on the trade of medicines will also increase the costs of drug production. Even with a trade deal, changes in the supply chain and potential costs of customs would increase costs [3]. Already during the transition period, no UK representatives can participate in EMA meetings [9]. A disconnect between the MHRA and the EMA could also limit data sharing. This would affect the United Kingdom's ability to effectively monitor the safety and efficacy of postapproval medicines [3,4]. The EU is also a leader in the monitoring of counterfeit drugs and global supply chains [10]. After Brexit, the United Kingdom could still be included but would have no influence to direct this monitoring [6]. This loss of influence and prestige in the pharmaceutical industry has already begun with the move of the EMA headquarters from London to Amsterdam [6].

Research is another area of concern for UK pharmaceutical companies and scientists, as not being an EU member state means the United Kingdom may no longer be eligible for EU research funding programs like Horizon 2020 [3]. Lack of inclusion in the EU could also affect clinical research trials. Pharmaceutical companies would have to register trials separately in the United Kingdom and the EU, and would require another authorization to recruit UK patients. These extra hurdles might make companies unwilling to use UK patients, which would deny patients early access to new treatments and make results less generalizable to UK populations [3,11].

The different forms that Brexit could take will influence its effect on the pharmaceutical supply chain. If a deal is established that allows the United Kingdom access to the single market, similar to the European Economic Area (EEA), or that keeps the MHRA integrated with EU health activities and negotiates free trade agreements with EU countries, the costs and availability of medicines are unlikely to be seriously affected, and the most severe consequence would likely be the loss of the United Kingdom's prestige in the pharmaceutical industry [1,6]. If the United Kingdom sets up free trade agreements but the MHRA is not involved with the EMA, there could be delays in market authorization approvals, loss of expertise in postapproval safety monitoring; delays in detecting and managing risks because of reduced communication and data sharing; and increased production costs to cover duplicate batch testing in the United Kingdom and EU [1,6]. A Brexit that applies WTO rules to UK-EU trade could result in medicine shortages because of the significant changes to the supply chain and largely increased costs due to tariffs [1,6]. Essentially, the more disconnected the United Kingdom becomes from the EU, the more severe the changes to the pharmaceutical supply chain and the potential health consequences [6]. The uncertainty of Brexit has meant that many companies are already preparing for worst-case scenarios, which means that consequences could be felt before Brexit occurs [1].

The uncertainty around Brexit has led to a variety of opinions, possible scenarios, and dire warnings of medicine shortages. However, a search of PROSPERO (International Prospective Register of Systematic Reviews) for "Brexit" and "Pharmaceutical" returns no results, and neither does a search for "Brexit" alone. This lack of reviews means that there is a need to aggregate all of the opinions and perspectives on the effect that Brexit will have on the pharmaceutical industry and assess the expected consequences and levels of concern about them. The scope of this review is adopted from a paper that uses the WHO Health System Framework [12] to structure its evaluation of how Brexit could affect UK health services [6]. Therefore, this review will focus on two main research questions. First, what are the potential consequences of Brexit

for the UK pharmaceutical supply chain (assessed according to the WHO system building blocks)? Second, to what extent is there agreement on the likelihood and severity of these potential consequences?

Methods

Overview

The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols Extension for Scoping Reviews) guidelines will be used to structure the review [13]. The scoping review will conduct a literature search, article selection, data extraction, quality appraisal, data analysis, and data synthesis.

Eligibility

Inclusion Criteria

We will include academic and grey literature published in 2016 or later. The year 2016 was chosen because that was the year of the Brexit referendum [14] and because the process of Brexit has been so uncertain that more recent publications are more likely to reflect current expected consequences. Both academic and grey literature are being considered because nonacademic sources such as company and institute reports and news articles are likely to have relevant information. Publications that discuss at least one potential effect of Brexit on the UK pharmaceutical supply chain will be included.

Exclusion Criteria

We will exclude publications that are not written in English and publications that do not focus on the effect of Brexit on the UK pharmaceutical supply chain specifically. We will focus exclusively on the United Kingdom to narrow the scope of the study. Publications, particularly from the grey literature, will also be excluded if they are not of high quality. The quality of grey literature will be assessed using the AACODS checklist [15], which examines whether certain criteria are present in the source. A value of 1 will be assigned to a "yes," and if the number of "yes" responses is less than half of the total possible, the source will be excluded [16].

Search Strategy

The following databases will be searched: MEDLINE, EMBASE, PsycINFO, Healthcare Management Information Consortium (HMIC), Cochrane, Web of Science, Business Source Complete, EconLit, Economist Intelligence Unit, and Nexis.UK. These will be accessed through the University of Oxford Search Oxford Libraries Online (SOLO) interface when possible. In addition, a Google search for grey literature such as opinion pieces, institute reports, press releases, and blog posts will be conducted. A combination of effort-bounded and evidence exhaustion criteria will be used to limit the Google search: the first 100 results will be screened, and if those near the end of the list are still providing new, relevant information, screening will continue up to the 200th result, or until sources cease to provide new information [16]. Key search terms were identified in a preliminary review of the literature, search strings were constructed, and databases were chosen in consultation with a librarian. Table 1 shows the search concept and keywords to be searched for this review. Databases will be searched for items published from the beginning of 2016 to the date of search.

Table 1. Search terms.

Category	MeSH terms	Keywords (in title or abstract)
Brexit	European Union, United Kingdom	Brexit OR United Kingdom OR Britain OR (("EU" OR "European Union") AND "single market") OR "Article 50" OR ((leave OR withdraw* OR exit OR remain OR stay) ADJ4 ("European Union" OR "EU" OR "EEA" OR "European Economic Area")) OR "Post-Brexit"
Pharmaceuticals	Drug industry, pharmaceutical preparations, pharmaceutical societies, pharmaceutical economics, drug approval, United States Food and Drug Administration	((Pharma* OR drug* or medic*) ADJ4 (industr* OR compan* OR supply OR sector OR production OR approval OR deliver* OR regulat* OR preparation* OR societ* OR econom* OR manufactur* OR shortage* OR stockpil* OR stock-pil*)) OR "EMA" OR "European Medicines Agency" OR "MHRA" OR "Medicines and Health products Regulatory Agency" OR "FDA" OR "Food and Drug Administration" OR "Royal Pharmaceutical Society" OR "National Health Service" OR "NHS" OR "Department of Health"
Effects	Cost and cost analyses, time-to-treatment	Consequence* OR change* OR outcome* OR effect* OR implication* OR result* OR opinion* OR cost* OR delay* OR "customs union" OR "free trade" OR "severe" OR "severity"

Screening and Article Selection

The citation management software Mendeley will be used to store articles and remove duplicates before screening. The titles and abstracts of all identified articles and grey literature sources will be screened by two independent reviewers to minimize selection bias. As grey literature does not always have an abstract, summaries or tables of contents will be screened for eligibility instead [17]. The full texts of articles and grey literature will then be read to determine final inclusion in the review. Disagreements between reviewers at both initial and full-text screening stages will be resolved with discussion. If no consensus can be reached, a third reviewer will make the final decision. Details of the screening and selection process will be recorded in a PRISMA flow diagram to ensure reproducibility.

Data Extraction

A table for data extraction will be set up with the predetermined outcomes. The primary outcome will be the expected

consequences of Brexit for the UK pharmaceutical supply chain. One reviewer will perform the data extraction from all of the papers, and a second reviewer will check the data extraction for all the full texts. Disagreements between the two reviewers will be resolved by discussion, and a third reviewer will be consulted if consensus cannot be reached. An initial review of the literature has suggested items to be extracted (Textbox 1), but other data identified during the review will be included if relevant.

Textbox 1. Data to be extracted from articles.

General study information

- Date of publication
- Type of source (eg, peer-reviewed article, institute report, press release)
- Demographics of authors (anything reported, including location, academic affiliation or workplace, age)

Effects of Brexit

- What form(s) of Brexit is (are) being considered?
- Consequences for the United Kingdom identified in the publication, including but not limited to the following: estimated costs of Brexit, estimated delays in production or availability of drugs, impact of delays and availability on health outcomes
- Reasons provided for expected consequences
- Severity of consequences expected by author(s)

Quality Appraisal and Risk of Bias Assessment

After the final selection of the studies, the risk of bias and quality of sources will be independently assessed by two reviewers. Disagreements in judgment will be discussed before consulting a third reviewer. Any randomized controlled trials that are included in the review will be assessed using the Cochrane Collaboration Risk of Bias tool [18]. The quality of other types of studies will be assessed using the relevant CASP checklists [19]. The quality of grey literature sources will be assessed using the AACODS checklist [15].

Data Analysis and Synthesis

Eligible sources will subsequently be reviewed in detail and data will be extracted, categorized, and recorded in a predesigned Excel spreadsheet (Microsoft Corp). A meta-analysis or statistical analysis is unlikely to be feasible, due to the anticipated variety of source types and reported outcomes, so we will conduct a descriptive analysis to summarize the extracted data. The discussion will synthesize the data to summarize the currently expected consequences of Brexit on the UK pharmaceutical supply chain and will assess the degree of agreement on the likelihood and severity of these consequences.

Results

The results will be included in the scoping review, which we aim to publish in 2020. The expected consequences reported by the publications (and their predicted severity) are anticipated to be conditional on the publications' expectations of the form Brexit will take (ie, how Brexit will unfold and what deal, if any, will be reached).

Discussion

A systematic and scoping review of academic and grey literature will increase clarity on the different ways Brexit might impact the UK pharmaceutical supply chain and the degree of agreement on the likelihood and potential severity of those consequences. As the situation around Brexit has been highly variable and unstable since the referendum in 2016, more recent publications (as well as those of higher quality) will be weighed more heavily when drawing conclusions. Additionally, any trends identified in how expected consequences have changed over time will be discussed in the context of the key points of the Brexit negotiations.

Understanding the potential consequences and their likelihood could help improve preparation for Brexit and could inform decisions on how to manage the change from the status quo to whatever the new relationship with the EU becomes. In the short-term, this has particular benefit for scientific advisors, negotiators, and policy makers, but in the long-term, the decisions they make when establishing the structure for new UK-EU relations will have significant effects on all stages of the pharmaceutical supply chain, which in turn will affect UK pharmaceutical companies, health care systems, and residents. Based on the data, this section will explore what conclusions can be drawn and with what degree of confidence, the limitations of the scoping review, and what directions future research should take.

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Authors' Contributions

EM, MMI, and CL conceived the study topic and designed the review protocol. MMI wrote the protocol with revisions from MVV and EM.

Conflicts of Interest

None declared.

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Abbreviations

AACODS: Authority, Accuracy, Coverage, Objectivity, Date, Significance
CASP: Critical Appraisal Skills Programme
EMA: European Medicines Agency
EU: European Union

HMIC: Healthcare Management Information Consortium
MHRA: Medicines and Health Products Regulatory Agency
WTO: World Trade Organization

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Original Paper

Work2Prevent, an Employment Intervention Program as HIV Prevention for Young Men Who Have Sex With Men and Transgender Youth of Color (Phase 3): Protocol for a Single-Arm Community-Based Trial to Assess Feasibility and Acceptability in a Real-World Setting

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Abstract

Background: In the United States, young cisgender men who have sex with men (YMSM), young transgender women (YTW), and gender nonconforming (GNC) youth face elevated rates of HIV infection. However, racial and ethnic disparities in adolescent HIV infection cannot be attributed to individual-level factors alone and are situated within larger social and structural contexts that marginalize and predispose sexual and gender minority youth of color to HIV. Addressing broader ecological factors that drive transmission requires interventions that focus on the distal drivers of HIV infection, including violence exposure, housing, food insecurity, educational attainment, and employment. Given the ways that economic instability may make YMSM, YTW, and GNC youth of color vulnerable to HIV exposure, this study focuses on employment as an HIV prevention intervention. More specifically, the intervention, called Work2Prevent (W2P), targets economic stability through job readiness and employment as a means of preventing behaviors and factors associated with adolescent and young adult HIV, such as transactional sex work and homelessness. The intervention was adapted from iFOUR, an evidence-based employment program for HIV-positive adults in phase 1 of this study, and pilot tested in a university-based setting in phase 2.

Objective: This paper aims to describe the protocol for the community-based test phase of W2P. The purpose of this phase was to pilot test a tailored, theoretically informed employment intervention program among YMSM, YTW, and GNC youth of color within a lesbian, gay, bisexual, transgender, and queer (LGBTQ) community setting.

Methods: The employment intervention was pilot tested using a single-arm pretest-posttest trial design implemented among a sample of vulnerable YMSM, YTW, and GNC youth of color using services within a community-based LGBTQ center. Assessments will examine intervention feasibility, acceptability, and preliminary estimates of efficacy.

Results: Phase 3 of W2P research activities began in May 2019 and was completed in December 2019. Overall, 41 participants were enrolled in the community-based pilot.

Conclusions: This study will assess intervention feasibility and acceptability in the target populations and determine preliminary efficacy of the intervention to increase employment and reduce vulnerability to HIV when implemented in a community-based setting serving LGBTQ youth of color. Testing the intervention in a community setting is an opportunity to evaluate how recruitment, retention, and other outcomes are impacted by delivery in a venue akin to where this intervention could eventually be used by nonresearchers. If W2P demonstrates feasibility and acceptability, a larger multisite trial implemented in multiple community settings serving YMSM, YTW, and GNC youth of color is planned.

Trial Registration: ClinicalTrials.gov NCT03313310; https://clinicaltrials.gov/ct2/show/NCT03313310

International Registered Report Identifier (IRRID): DERR1-10.2196/18051

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KEYWORDS

HIV/AIDS; youth; young men who have sex with men; YMSM; young transgender women; YTW; gender nonconforming youth; LGBTQ; unemployment; homelessness; sex work

Introduction

Background

In the United States, youth of color assigned male at birth who engage in sexual contact with individuals assigned male at birth, including young cisgender men who have sex with men (YMSM), young transgender women (YTW), and gender nonconforming (GNC) youth, face elevated rates of HIV infection [1,2]. In 2018, an estimated 26% of all new HIV diagnoses were among Black men who have sex with men (MSM), while 20% were among Hispanic/Latino MSM [1]. These outcomes are stark, given that Black and Latino individuals comprise 13% and 18% of the US population, respectively [3]. Further, although the Centers for Disease Control and Prevention (CDC) does not provide estimates of HIV infection for transgender and GNC populations due to gaps in public health department data, a previous meta-analysis of US studies found an average HIV prevalence rate of 28% among transgender women, with a higher rate of 56% among Black transgender women specifically [4]. This racial disparity is not solely driven by individual sexual behaviors, but rather a number of interrelated socioecological and structural factors that proximate YTW, GNC youth, and YMSM of color to HIV exposure and disease susceptibility [2,5-11]. In particular, these groups face co-occurring and interconnecting disparities in housing, health care access, social service availability, education, poverty, employment, and violence [12-21]. Economic factors may be especially salient among these populations, as prior research suggests that sexual and gender minority youth of color face hiring bias, job discrimination, low pay, and limited benefits when navigating employment [18,22]. These experiences contribute to a large proportion of sexual and gender minority youth of color living in poverty [18,22-24].

Additionally, economic marginalization may increase potential for HIV exposure and infection by contributing to reliance on survival sex work, or exchanging sex for money, food, shelter, drugs, or other commodities [25-27]. Survival sex work has also been associated with coping-related substance use [12,13,17,20,21]. Previous studies have found that engagement with survival sex work among YMSM, YTW, and GNC of color is also associated with structural factors, including financial insecurity and socioeconomic disconnection [28-30]. Further, engagement in survival sex work may increase youths' susceptibility to sexually transmitted infections (STIs) and HIV infection by exposing them to sexual networks with higher STI and HIV prevalence, increasing their numbers of sexual partners, and creating challenges in condom use negotiation [28-30].

Given the role that economic instability may play in driving HIV susceptibility among YMSM, YTW, and GNC youth of color, structural interventions are needed in order to address HIV inequities at their root cause [31]. Structural-level interventions target underlying social drivers of poor health and promote agency among marginalized groups in order to facilitate health-positive actions that can benefit both the individual and community [31]. More specifically to HIV, structural interventions, including comprehensive sex education, community- and venue-based HIV/STI testing, stable housing programs, increased health care coverage, and needle exchange programs, have greatly reduced HIV infection [32-34]. However, fewer structural interventions that address distal drivers of HIV infection, including decreased criminalization and poverty and increased economic stability, have been developed and implemented, although these factors have the potential to mitigate broader disparities in HIV [33,34]. Accordingly, employment as HIV prevention has the potential to be a scalable intervention that targets the economic drivers of HIV infection among YMSM, YTW, and GNC youth.

Rationale for Employment as HIV Prevention

In a recent Chicago-based social network intervention for Black YMSM and YTW aged 18 to 35 years, roughly 45% of participants from the respondent-driven sample reported being unemployed [35]. Across Adolescent Medical Trials Network for HIV/AIDS Interventions (ATN) sites in 17 US cities, 64.6% of adolescents and young adults reported being unemployed,

despite 67.8% having completed high school and being a mean working age of 20.4 years [36]. Thus, many youths vulnerable to HIV may benefit from a tailored intervention that specifically addresses job preparedness and workforce engagement [18,22,37]. Additionally, employment interventions may also need to specifically address the experiences of overt and implicit discrimination and mistreatment that sexual and gender minority youth report while job seeking and within the workplace [38-40].

The objective of the Work2Prevent (W2P) study is to adapt and pilot test Increased Individual Income and Independence (iFOUR), an effective, theoretically-driven employment program for HIV-positive adults [41-44], to the needs of vulnerable YMSM, YTW, and GNC youth of color aged 16 to 24 years. For a full rationale of the overall W2P study, please refer to the W2P phase 2 paper [45].

Theoretical Framework

The W2P study is informed by frameworks from the health belief model [46] and positive youth development [47-49]. More specifically, the W2P intervention is intended to help participants identify barriers to obtaining employment and increase positive beliefs regarding the perceived benefits of employment. This is supported by helping young people understand, value, and develop both external and internal assets that will benefit their pursuit and maintenance of stable, formal employment. For a more thorough explanation of the theoretical framework, please refer to the W2P phase 2 paper [45].

Rationale for Testing the Intervention in a Community Setting

Phase 3 of the W2P study, the topic of this current paper, focuses on pilot testing the intervention in a community-based social service setting. Implementation science highlights the importance of implementing and evaluating interventions in community settings that more closely reflect the real conditions under which the intervention will be delivered upon being scaled [50-53], given that interventions may perform differently when translated from a university research setting to a community-based organization or clinic [54-56]. Further, community-based interventions are increasingly recognized as essential to achieving the Joint United Nations Programme on HIV/AIDS 90-90-90 targets through their ability to overcome structural barriers to health care access [57]. For example, a community-based implementation of Many Men, Many Voices, a CDC-endorsed evidence-based health intervention for Black MSM, evidenced greater reductions in HIV-related behaviors than in the original randomized trial [58,59]. In translating an intervention from a university setting to a community setting, researchers may identify necessary adaptations and challenges that must be considered to maintain the utility of the intervention. Therefore, in order to ensure that efficacious HIV interventions may be optimally scaled, it is important to implement and evaluate these interventions in community-based clinics and organizations [60].

Assessing how interventions perform in a community setting may be particularly important for interventions that employ a structural-level focus. Indeed, social and structural outcomes are often interrelated. For instance, a previous study of transgender women of color found that employment status was associated with stable housing [61]. Further, the impact of unemployment and job loss on mental health has been well documented [62], often leading to poor mental health outcomes [63] and maladaptive health behaviors [64]. When structural-level interventions are delivered in a university setting, they are generally delivered in isolation and thus do not directly consider how the intervention may interact with services aimed at addressing other related structural factors. However, when an intervention is integrated into an existing service-providing organization, other services that address related structural needs are generally more readily available to study participants. Thus, evaluation of structural-level interventions in community-based settings allows researchers to better assess how intervention performance may be impacted by the social ecology of existing organizations and their corresponding service apparatuses.

Evaluating interventions in community settings, particularly those tailored for marginalized groups, may also be necessary because organizational settings can have an impact on participants' level of trust and engagement. Due to historical events, like the Tuskegee syphilis study, and negative experiences with the health system [65], many people of color are reluctant to take part in health research [66]. Further, university settings are often unknown to study participants prior to enrollment and thus, initial impressions of the organizations delivering the intervention may be less established. In contrast, delivery of interventions in community organizations and clinics familiar to participants leverages existing relationships in order to make the intervention more reputable to the community. Further, the presence of familiar individuals who vouch for the trustworthiness of the researchers has the potential to decrease mistrust and engender greater participation in an intervention [67]. Understanding how this impacts study participants' engagement and the performance of the intervention may be critical in ensuring potential scalability. This may be particularly important for interventions targeting sexual and gender minority youth of color, who often express high levels of institutional and medical distrust due to longstanding and historical mistreatment [68,69].

Implementing and evaluating interventions in community settings may also allow researchers to assess how intervention delivery is impacted by real-world logistical concerns [53,70]. In order to implement an intervention in a community setting, it may need to be further tailored to accommodate organizational constraints such as staffing, space, scheduling, technological capacity, and resource supports [53]. Testing an intervention in a community-based organization allows researchers to tailor the intervention to address these real-world constraints and assess how this additional tailoring impacts intervention performance.

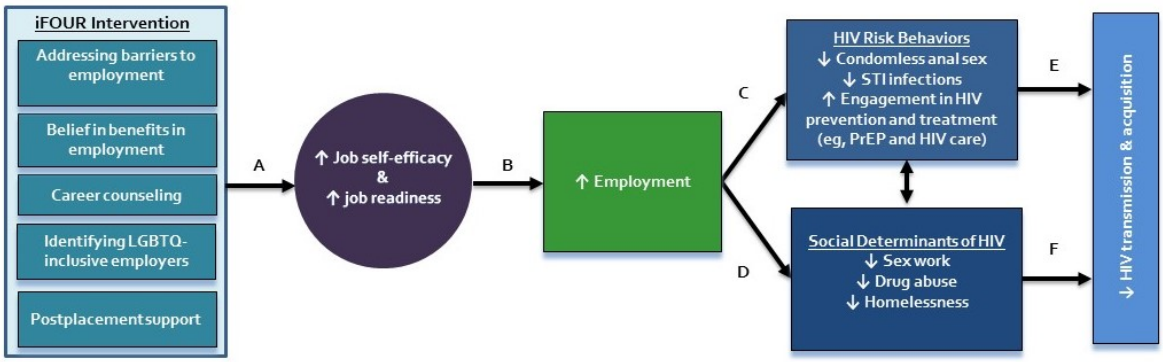
Methods

Conceptual Model

The W2P conceptual model in Figure 1 draws on the existing iFOUR theoretical framework to hypothesize the potential relationship between adolescent and young adult employment and HIV. The W2P model proposes that employment and

subsequent economic connection and stability serve as a structural-level intervention for adolescents and young adults. Our hypothesis is that the adapted and tailored iFOUR intervention will facilitate increased job self-efficacy and job readiness (path A) and ultimately increase employment placement and maintenance (path B). Further, establishing economic stability will decrease engagement in HIV-related behaviors and increase HIV prevention and care (path C), while also decreasing involvement with known social determinants of HIV, such as sex work and substance use (path D), which are directly linked to HIV transmission and acquisition among YMSM, YTW, and GNC youth of color (paths E and F).

Figure 1. W2P conceptual model. iFOUR: Increased Individual Income and Independence; LGBTQ: lesbian, gay, bisexual, trangender, and queer; PrEP: pre-exposure prophylaxis; STI: sexually transmitted infection; W2P: Work2Prevent.



Study Design

W2P uses a mixed methods design. Phase 1 involved the adaptation of relevant intervention components from the existing evidence-based iFOUR employment program for HIV-positive adults [41-43] to YMSM, YTW, and GNC youth of color. Phase 2 involved a pretest of the intervention and study assessments, followed by pilot testing in a university setting to assess feasibility and acceptability and to provide preliminary estimates of efficacy using pretest-posttest comparisons. Phase 3 consists of further refinement of the intervention and study assessments, as well as pilot testing of the intervention in a community-based setting in order to further assess feasibility and acceptability and to provide preliminary estimates of intervention efficacy under real-world conditions using pretest-posttest comparisons. For the purposes of adaptation to a community setting, a number of changes were made between phase 2 and phase 3, including condensing the survey instruments, workshop sessions, and intervention timeline. In phase 2, the intervention workshops were delivered over 2 weeks, and the participants generally completed the baseline survey during a separate study visit within 3 weeks prior to the first intervention session. In phase 3, the intervention workshops were delivered over the course of 2 days, and the first session was offered immediately after participants complete the baseline assessment. In phase 2, participants completed a follow-up visit at 8 months, whereas the follow-up visit was at 3 months for phase 3. For a complete description of phase 2, please refer to the W2P phase 2 protocol paper [45].

Ethics, Consent, and Institutional Board Approval

W2P has been reviewed and approved by the University of Chicago Institutional Review Board (IRB# 16-1152). Informed consent for this study was obtained in person by study staff before any study-related activities took place. The trial was registered in October 2017 at Clinicaltrials.gov (NCT03313310).

Participants

Study participants included 41 Black or African American and Hispanic or Latinx YMSM, YTW, and GNC youth. Inclusion criteria included (1) being assigned male at birth, (2) reporting ever having sex with men, (3) identifying as African American or Black or Hispanic or Latinx, (4) aged 16 to 24 years, (5) English speaking, (6) currently unemployed but seeking employment or employed only part-time, defined as working 35 hours or less on average per week, (7) able to attend a 4-session workshop, and (8) did not participate in phase 2 of W2P.

Study Setting

All study visits were conducted at a community site, the Village. The Village is a community-based setting that provides drop-in services, support groups, resources, behavioral health counseling, community programs, housing and legal assistance, and HIV and STI testing to sexual and gender minority youth. The Village is affiliated with the Chicago Center for HIV Elimination at University of Chicago Medicine and primarily serves Black YMSM, YTW, and GNC youth. This community space is located on the south side of Chicago, a predominantly Black and African American area of the city. A previous spatial study found this area was lacking in career services tailored to the lesbian, gay, bisexual, transgender, and queer (LGBTQ) community [19]. The Village serves approximately 1000 individuals annually, of which 90% are Black or African American, 9% are Hispanic or Latinx, 74% are MSM, 7% are transgender, and 36% are adolescents and young adults aged 24 and younger.

Recruitment

Planned participant recruitment efforts included recruitment from the community site itself, as well as from primary and community clinics serving YMSM, YTW, and GNC youth, such as Howard Brown Health, a Chicago-based LGBTQ-focused Federally Qualified Health Center, during

their youth drop-in programs. Interested participants completed a prescreen survey to assess eligibility. Eligible participants were then scheduled for study visits and workshop sessions.

Incentives

Study participants were offered compensation for their time. Participants could receive up to US $290 total for complete participation in the form of cash or Visa gift card equivalents. Participants received US $30 for each study visit completed at baseline, postintervention, and 3-month follow-up, up to US $40 for biological specimens at baseline and 3-month follow-up, if provided, and US $30 for each workshop session attended.

Visit Schedule and Data Collection

W2P consisted of data collection across 3 time points, which occurred at baseline, postintervention, and 3-month follow-up, as referenced in Figure 2. A 4-session intervention workshop series occurred over a 2-day period, with workshop sessions 1 and 2 being conducted on the same day as the baseline visit and sessions 3 and 4 on the same day of the postintervention visit.

Figure 2. Study procedures. ACASI: audio computer-assisted self-interview.

Study procedures	Baseline visit	Postintervention visit	Month 3 follow-up visit
HIV/STI testing	✓		✓
Substance use screening	✓		✓
ACASI survey	✓	✓	✓
Workshop sessions 1 and 2	✓		
Workshop sessions 3 and 4		✓	

Baseline

Participants completed informed consent and then confirmed eligibility. Subsequently, participants complete an audio computer-assisted self-interview (ACASI) survey using an iPad (Apple Inc). Survey items included questions pertaining to demographics, sexual behaviors, HIV risk behaviors, relationships, employment, income, substance use, and other structural variables such as homelessness, food insecurity, and health care use. Optional biologic samples were collected from participants who consented to them. These samples included a finger stick for rapid HIV testing using the Determine HIV-1/2 Ag/Ab Combo (Alere Inc), a urine sample for drug screening and chlamydia and gonorrhea testing, and anal and oral swabs for chlamydia and gonorrhea testing.

Intervention

Participants completed a 4-session intervention workshop adapted from the existing iFOUR program [41-43] and piloted in phase 2 of W2P. In phase 3, workshop sessions occurred over a 2-day period, with 2 sessions on each day. Session 1 focused on goal setting and identifying strengths; session 2, on communication, networking, and job searching; session 3, on balancing work with health and wellness; and session 4, on preparing job application materials and interview preparation. For a full description of the process for determining these intervention components, please refer to the W2P phase 1 protocol paper [71].

Workshop sessions were delivered by 2 facilitators in groups of 6 to 12 participants across the course of 2 days, with 2 sessions per day. The W2P Career Readiness Workbook was used as a guide for all workshop sessions and given to all study participants at the first session. Facilitators used an annotated W2P Facilitator Guide that provides detailed instruction on delivery of the intervention curriculum. During each session, facilitators completed a fidelity assessment to help ensure fidelity to the W2P Career Readiness Workbook, and after each session, they completed a workshop debriefing form to capture any workshop notes or comments.

Postintervention

Once participants completed the workshop sessions, they completed a postintervention ACASI survey using an iPad. Survey items included questions on workshop evaluation, job-seeking self-efficacy, and pre-exposure prophylaxis and HIV testing use.

3-Month Follow-up

The final study visit occurred 3 months after the intervention was completed. During this visit, participants completed the baseline ACASI survey using an iPad and provided repeat biologic samples, if they consented to them.

Outcomes

Primary Outcomes

The primary outcomes of this study are (1) information systems success model (ISSM) score, (2) workshop completion, (3) change in job-seeking self-efficacy scale score, and (4) change in protean career attitudes (PCA) scale score.

First, the ISSM will be used to assess for intervention acceptability and satisfaction. The 21-item scale yields a total score and measures 4 subdomains: information quality, handbook quality, perceived usefulness, and overall satisfaction. This scale has been adapted from Horvath et al [72].

Second, workshop completion will be used to assess intervention feasibility. Workshop or intervention completion is defined as having attended at least two of the 4 workshop sessions and is measured by tracking participant attendance.

Third, job-seeking self-efficacy is defined as one's perceived ability and confidence to perform job search and application activities. The 12-item job-seeking self-efficacy scale by Barlow et al [73] yields a total score in which higher values indicate higher self-efficacy. Job-seeking self-efficacy was previously found to be associated with employment in a previous study of transgender women of color [61].

Fourth, PCAs are defined as self-direction in the pursuit of success in one's work. Protean career attitudes have previously been found to be associated with positive career satisfaction and self-perceived success [74]. The validated 7-item scale by Porter et al [75] yields a total score and measures 2 subdomains: self-directed attitudes and values-driven attitudes.

Secondary Outcomes

Secondary outcomes include (1) change in self-reported hours worked per week, (2) change in self-reported sexual risk behaviors, (3) change in chlamydia test result, (4) change in gonorrhea test result, and (5) reactive HIV test.

First, hours worked per week was self-reported at baseline and at the 3-month follow-up visit. Change in hours worked per week from the baseline to the 3-month follow-up will be used to assess change in employment status.

Second, sexual risk behaviors are defined as self-reported engagement in the following behaviors during the previous 3 months [76]: (1) condomless anal intercourse (receptive or insertive) with cisgender male partner of unknown HIV status, (2) anal intercourse (receptive or insertive) with at least 3 cisgender males, (3) sex with cisgender male partner with an STI, (4) condomless anal intercourse (receptive or insertive) with HIV-positive cisgender male partner, (5) anal intercourse (receptive or insertive) with condom failure, and (6) transactional sex work involvement. The previous 3 months refers to the 3 months prior to the baseline visit for the first assessment and the 3 months prior to the 3-month follow-up visit for the second assessment. Change in sexual risk behaviors is defined as the change in self-reported behaviors from baseline to the 3-month follow-up.

Third, prevalence of chlamydia infections was assessed at baseline and 3-month follow-up using oral, anal, and urine samples. Each of the 3 tests yields a positive or negative result. Change in chlamydia test result is defined as the change from baseline to the 3-month follow-up. Oral, anal, and urine tests are treated as separate outcomes.

Fourth, prevalence of gonorrhea infections was assessed at baseline and 3-month follow-up using oral, anal, and urine samples. Each of the 3 tests yields a positive or negative result. Change in gonorrhea test result is defined as the change from baseline to the 3-month follow-up. Oral, anal, and urine tests are treated as separate outcomes.

Fifth, testing for reactive or nonreactive HIV was assessed at baseline and 3-month follow-up. The reactive HIV test outcome uses the 3-month follow-up result.

Power

Given the exploratory nature of this study and limited access to this population, the analyses are not designed to have a specified level of statistical power. A repeated measures pretest-posttest design will be used to reduce the variability in the estimate of the treatment effect.

Statistical Analysis

The analytic plan will estimate preliminary efficacy of the intervention by comparing preassessments and postassessments of employment and sexual risk behaviors. Descriptive statistics will be used to analyze the proportions and central tendencies for participant sociodemographic characteristics collected in the surveys. We will first generate frequencies, means, and other measures of central tendency as appropriate to describe our sample and outcomes at each of the 3 time points: baseline, postintervention, and 3-month follow-up.

All participants who were enrolled at baseline and completed the baseline ACASI will be included in the primary and secondary analyses as applicable. Analysis population participants will be included in all primary and secondary analyses for which their data for the specified outcome are not missing. Participants who did not attend any workshop sessions will not be included in analyses involving workshop evaluation. Primary analyses will assess intervention acceptability, satisfaction, and feasibility, as well as change in job-seeking self-efficacy and PCA score. Secondary analyses will evaluate the intervention by comparing preintervention and postintervention employment and sexual risk behaviors.

Changes in primary and secondary outcomes between baseline and 3-month follow-up will be assessed using paired 2-tailed *t* tests for continuous variables (eg, ISSM, job-seeking self-efficacy, and PCA scores) and the McNemar test for matched categorical variables (eg, STI results). We will use standard diagnostic tools to assess the appropriateness of the normality assumption and, if approximate normality of the residuals is not tenable, a nonparametric test for continuous paired data (ie, Wilcoxon signed rank test) will be used. All hypothesis testing will be performed at an α level of .1, given the exploratory nature of the study. To the extent that data allow, multivariable analyses will adjust for sociodemographic characteristics, workshop attendance, baseline employment status, and study completeness. Analytical models will include linear regression or generalized linear models for continuous outcomes and logistic regression for binary outcomes.

Analysis of the primary and secondary outcomes are described in detail within the statistical analysis plan, which will be accessible on ClinicalTrials.gov once study results have been entered.

Results

Phase 3 of W2P research activities began in May 2019 and was completed in December 2019. Overall, 41 participants were enrolled in the community-based pilot.

Discussion

Interventions that address the complex socioecological factors that make YMSM, YTW, and GNC youth of color vulnerable to HIV are necessary to curb the epidemic in this population. Given the role of social determinants of health in HIV infections experienced by these young people, interventions must explicitly address factors such as unemployment, homelessness, and survival sex work in order to maximize the impacts of individual-level behavior changes intended to mitigate vulnerability for adolescent and young adult HIV.

In the first 2 phases of W2P, the intervention was adapted from iFOUR, tailored to YMSM, YTW, and GNC youth of color, and then evaluated in a university setting. The goal of phase 3 of W2P is to pilot test this structural-level employment intervention in a community-based setting that serves the target population. Testing the intervention in a community setting is an opportunity to evaluate how recruitment, retention, and other outcomes are impacted by delivery in a venue more akin to where this intervention could eventually be used by nonresearchers. Given recent findings that identify the south side of Chicago as largely lacking services targeting LGBTQ communities' specific needs [18], the selected site approximates well the most likely venue where this kind of intervention could be received by members of the target population. Further, by virtue of the study recruiting from and delivering the intervention in a community-based clinic that provides a range of supportive services, such as housing assistance, counseling, and HIV/STI testing, participants are in closer proximity to resources targeting a range of social determinants of health.

Given that the intervention was delivered to YMSM, YTW, and GNC youth of color in an urban LGBTQ community setting, deployment of the intervention in suburban or rural communities may require additional adaptation and refinement. Although implementing the employment intervention in an LGBTQ community–based setting offers an opportunity for direct recruitment and enrollment, the intervention may not reach YMSM, YTW, and GNC youth of color who are not connected with LGBTQ community and social services. Thus, additional approaches may be needed to reach the most vulnerable youth who are experiencing socioeconomic hardship.

If W2P demonstrates feasibility and acceptability when delivered in a community-based setting, we plan to test the efficacy in a multicity longitudinal trial across the ATN study sites. Phase 3 of W2P tested the intervention in one community venue. A scale-up of the project will allow the intervention to be tested in a range of community venues that may differ in ways that are relevant to outcomes, such as space, staff experience with intervention delivery, or availability of other resources. This will be an opportunity to further assess efficacy and identify implementation challenges and opportunities. If W2P demonstrates efficacy in the multicity trial, the intervention could be an asset for community organizations invested in addressing the role of employment in the HIV epidemic. Further, this intervention, which has been tailored to the target community and evaluated in relevant community-based settings, will provide YMSM, YTW, and GNC youth of color a way to gain employment skills needed to improve their economic situation and reduce HIV transmission.

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Conflicts of Interest

None declared.

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Abbreviations

ACASI: audio computer-assisted self-interview
ATN: Adolescent Medicine Trials Network for HIV/AIDS Interventions
CDC: Centers for Disease Control and Prevention
GNC: gender nonconforming
iFOUR: Increased Individual Income and Independence
ISSM: information systems success model
LGBTQ: lesbian, gay bisexual, transgender, and queer
MSM: men who have sex with men
PCA: protean career attitudes
STI: sexually transmitted infection
W2P: Work2Prevent
YMSM: young men who have sex with men
YTW: young transgender women

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Protocol

Pre-Exposure Prophylaxis Integration Into Family Planning Services at Title X Clinics in the Southeastern United States: Protocol for a Mixed Methods Hybrid Type I Effectiveness Implementation Study (Phase 2 ATN 155)

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Abstract

Background: Adolescent and young adult women (AYAW), particularly racial and ethnic minorities, in the Southern United States are disproportionately affected by HIV. Pre-exposure prophylaxis (PrEP) is an effective, scalable, individual-controlled HIV prevention strategy that is grossly underutilized among women of all ages and requires innovative delivery approaches to optimize its benefit. Anchoring PrEP delivery to family planning (FP) services that AYAW already trust, access routinely, and deem useful for their sexual health may offer an ideal opportunity to reach women at risk for HIV and to enhance their PrEP uptake and adherence. However, PrEP has not been widely integrated into FP services, including Title X–funded FP clinics that provide safety net sources of care for AYAW. To overcome potential implementation challenges for AYAW, Title X clinics in the Southern United States are uniquely positioned to be focal sites for conceptually informed and thoroughly evaluated PrEP implementation science studies.

Objective: The objective of this study is two-fold: to evaluate multilevel factors associated with the level of PrEP adoption and implementation (eg, PrEP screening, counseling, and prescription) within and across 3 FP clinics and to evaluate PrEP uptake, persistence, and adherence among female patients in these clinics over a 6-month follow-up period.

Methods: Phase 2 of Planning4PrEP (Adolescent Medicine Trials Network for HIV/AIDS Interventions 155) is a mixed methods hybrid type 1 effectiveness implementation study to be conducted in three clinics in Metro Atlanta, Georgia, United States. Guided by the Exploration, Preparation, Implementation, and Sustainment framework, this study will prepare clinics for PrEP integration via clinic-wide trainings and technical assistance and will develop clinic-specific PrEP implementation plans. We will monitor and evaluate PrEP implementation as well as female patient PrEP uptake, persistence, and adherence over a 6-month follow-up period.

Results: Phase 2 of Planning4PrEP research activities began in February 2018 and are ongoing. Qualitative data analysis is scheduled to begin in Fall 2020.

Conclusions: This study seeks to evaluate factors associated with the level of PrEP adoption and implementation (eg, PrEP screening, counseling, and prescription) within and across 3 FP clinics following training and implementation planning and to evaluate PrEP uptake, persistence, and adherence among female patients over a 6-month follow-up period. This will guide future strategies to support PrEP integration in Title X–funded clinics across the Southern United States.

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International Registered Report Identifier (IRRID): DERR1-10.2196/18784

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KEYWORDS

HIV; pre-exposure prophylaxis; implementation science; family planning services

Introduction

Adolescent and young adult women (AYAW) in the Southern United States are disproportionately affected by HIV in comparison with AYAW residing in other regions [1]. Southern states account for nearly half of the new HIV diagnoses, despite having only 37% of the nation's population [2]. In Atlanta, 4 metro counties (Cobb, DeKalb, Fulton, and Gwinnett) were identified as critical HIV hotspots in the Health and Human Services' *Ending the HIV Epidemic: A Plan for America* [3]. Reducing HIV among women in the Southern United States in general, and Metro Atlanta specifically, is a priority.

Since approval of daily oral PrEP as an effective HIV prevention strategy [4], there has been wide-scale endorsement to bring PrEP to scale through dissemination and implementation efforts in the United States [5-7], but PrEP remains underutilized in women relative to need [8-10]. The first steps in PrEP adoption are ensuring that those who can benefit from PrEP are aware of it and ensuring PrEP is accessible in health care settings where they seek care [11,12]. However, there is low knowledge of PrEP among US women [13-18] and women's health providers [19], although studies suggest that family planning (FP) providers are willing to prescribe PrEP once trained [19], and women are interested in taking PrEP once informed [20,21].

Anchoring PrEP delivery to health services such as FP clinics that AYAW already trust, access routinely, and deem useful for their sexual health is of great appeal. FP providers in areas with high HIV incidence are ideal potential PrEP providers because most (60%) AYAW utilize and trust FP providers for sexual health and preventative services [22]. Many are also important safety net sources of care for AYAW, particularly in states that did not expand Medicaid and are expected to offer HIV prevention services as part of quality FP [23].

However, PrEP has not been widely integrated into FP services in the United States. Our 2018 survey among individuals working in Title X clinics across the Southern United States revealed that the majority (approximately 80%) reported working in clinics that did not provide PrEP [24]. Our findings are in line with a 2015 national survey of FP providers in the United States, which reported low PrEP knowledge and use, especially in the South [19]. In addition, women have lower PrEP uptake and persistence than men [25], highlighting that significant implementation challenges exist among women.

Very few models exist that describe the organizational processes and strategies associated with successful integration of PrEP delivery in new clinic settings and none, to our knowledge, exists for FP clinics, including those supported by Title X funding. Despite the presence of clinical trial efficacy data for PrEP among both men and women, *real-world* effectiveness data on PrEP among women have only become recently available from studies among women in sub-Saharan Africa [26], thus lagging behind PrEP effectiveness research in men. Effectiveness-implementation hybrid designs are innovative implementation science approaches for more rapid *research to practice* translations. The hybrid type 1 design is a blended design that is ideally suited to test the effects of a clinical intervention on relevant patient outcomes in *real-world* settings (eg, PrEP uptake, adherence, and persistence among women) while gathering information on its implementation [27]. Given the aforementioned gaps in the literature on both effectiveness and implementation of PrEP among women in the United States, research employing a hybrid type 1 design is ideal for advancing the knowledge in this critical but understudied area and may inform future interventions to optimize PrEP delivery in this setting. Finally, maximizing the potential benefits of PrEP requires understanding the key provider- and patient-related steps in integrated PrEP delivery. These steps comprise the PrEP engagement cascade and have been proposed as a conceptual framework to identify and understand the key steps needed to maximize the benefits of PrEP [28-30]. However, there is a dearth of research exploring factors associated with these provider- and patient-related steps among women utilizing FP clinics in the Southeastern United States.

The Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) is a research program that aims to defeat the rising HIV epidemic among adolescents and young adults in the United States. The overarching goal of the ATN is to increase awareness of HIV status in youth and, for those diagnosed with HIV, increase access to health care. The ATN develops and conducts behavioral, community-based, translational, therapeutic, microbicide, and vaccine trials in youth who are at risk for or living with HIV, with a focus on the inclusion of minors. Our study is funded as part of the ATN (ATN 155). The combined findings and resulting tools and trainings will be valuable for PrEP integration in Title X–funded or similarly structured FP clinics and to inform future interventions to optimize PrEP delivery for AYAW. Phase 2 of Planning4PrEP was directly guided by phase 1 of the study; review phase 1 protocol paper for complete details [31]. In this

paper, we describe only the research protocol for the phase 2 study. The objective of this study is to evaluate multilevel factors associated with the level of PrEP adoption and implementation within and across 3 FP clinics and to evaluate PrEP uptake, persistence, and adherence among female patients in these clinics over a 6-month follow-up period.

Methods

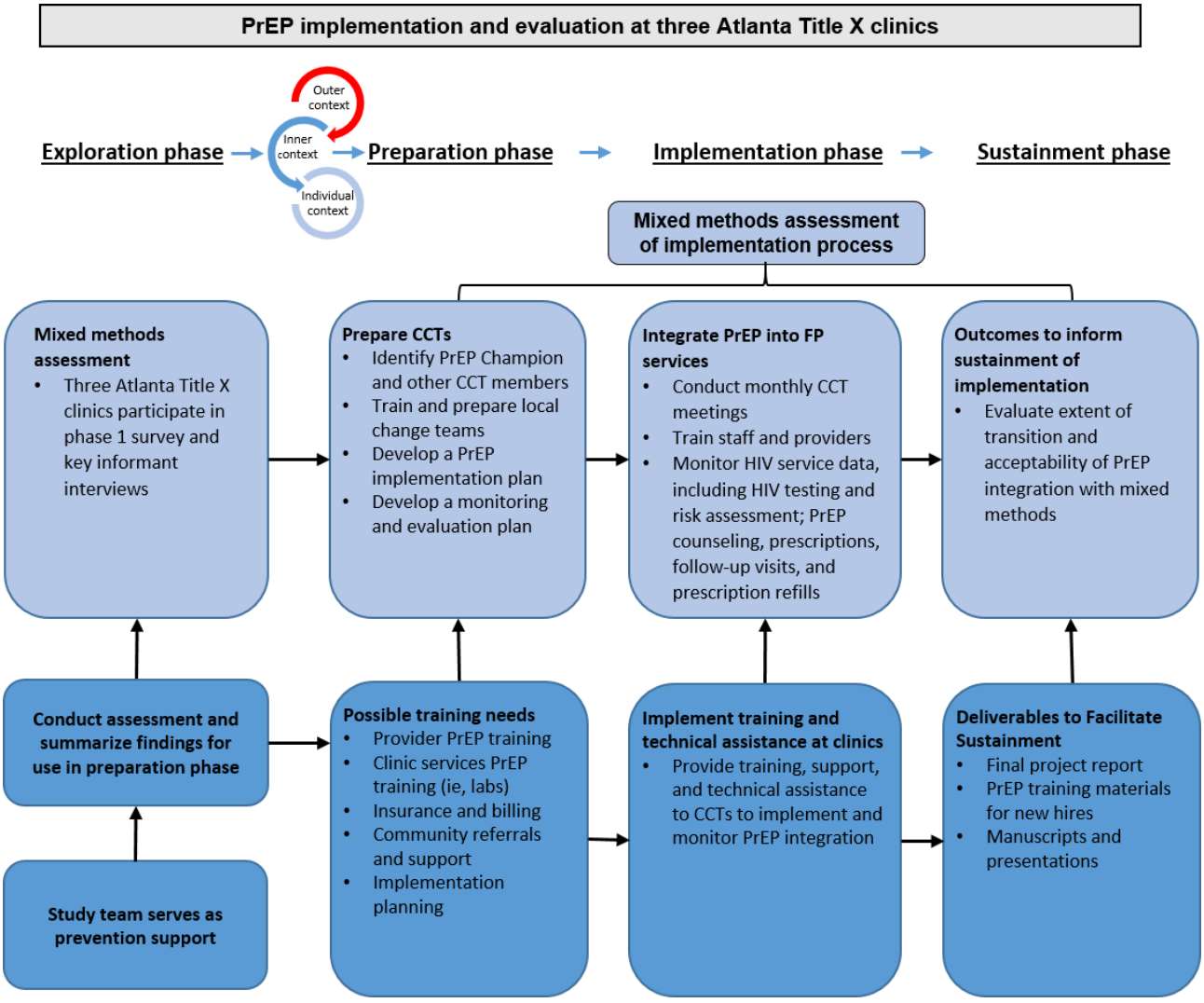
Study Design

This study is a mixed methods hybrid type 1 effectiveness implementation study with two key objectives. Objective one is to evaluate factors associated with clinic-level PrEP adoption and implementation at three FP clinics. This objective will be measured both quantitatively and qualitatively. Quantitative data include clinic-level aggregate data obtained via chart abstraction, staff-level data obtained via a web-based survey, and patient-level data collected via interviewer-assisted exit surveys. In addition to the web-based survey, staff participants will also take part in key informant interviews and focus groups.

Objective two is to evaluate the effect of PrEP integration on PrEP uptake, persistence, and adherence among female patient participants over a 6-month period. This objective will be measured via a prospective cohort study of 300 PrEP-eligible women across all three clinics. To characterize each step in the PrEP cascade, within this cohort, we aim to recruit women who may benefit from PrEP (as determined via HIV risk assessment by the patient or provider), regardless of whether PrEP was prescribed.

Both objectives directly correlate to different stages of the Exploration, Preparation, Implementation, and Sustainment (EPIS) framework (Figure 1). Methods pertinent to objective one fall under preparation, implementation and sustainment phases, whereas methods pertinent to objective two fall under the implementation and sustainment phases. Importantly, objective two methods are essential for better understanding real-world PrEP effectiveness among women in the United States. Secondary outcome measures among staff participants will be mapped to the Consolidated Framework for Implementation Research (CFIR) framework.

Figure 1. Pre-exposure prophylaxis implementation and evaluation process at three Atlanta Title X clinics including a federally qualified health center clinic, specialized family planning clinic, and hospital-based family planning clinic. CCT: Clinic Change Team; FP: family planning; PrEP: pre-exposure prophylaxis.



Theoretical Frameworks

EPIS Framework

The EPIS framework [32] is a phased, multilevel (ie, clinic and provider and staff-level) approach to conceptualizing implementation research that provides both structure and a process to implementation across 4 distinct stages. *Exploration*, the first stage, was assessed in the first phase of this study [31]. The next step, *preparation*, involves bringing together relevant stakeholders in a planning process to support effective implementation and includes developing a proposed plan to address barriers (eg, through clinic-wide PrEP trainings and capacity building with local PrEP technical assistance providers). The *implementation* stage begins after training or when other system changes are required for the PrEP end. When implementation reaches normalized operations (eg, a clinic can onboard a new provider and ensure that they are prepared to screen and provide PrEP), *sustainment* begins. This study will thoroughly evaluate EPIS stages from *preparation* to the early *sustainment* stage.

CFIR

Using the CFIR framework [33], we will assess which inner and outer contextual factors (barriers and facilitators) influence the level of adoption of PrEP services in Title X clinics serving women in the Southern United States. The CFIR provides a menu of constructs that have been identified as important for implementation success [33]. The CFIR captures the complex, multilevel nature of implementation and posits that successful implementation of a new innovation (PrEP delivery in FP clinics) will likely require the use of multiple strategies (eg, training, technical assistance, and an internal champion) at multiple levels of the implementation context. The CFIR comprises 39 constructs organized into 5 domains (intervention characteristics, outer setting, inner setting, characteristics of individuals, and process).

Consent and Institutional Review Board Approval

Given the various types of study participants (patients and clinic staff), phase 2 of this study was divided into two parts for logistical and institutional review board (IRB) purposes. Both parts have been reviewed and approved by the Emory University IRB (IRB# 00107692 and 00111612) and the University of North Carolina at Chapel Hill IRB (IRB# 18-2442 and 19-1784).

Written consent for the clinic staff focus groups, clinic staff web-based surveys, clinic patient surveys, and cohort study will be obtained for all willing participants before participation. Among the web-based survey participants, written consent is asked within the survey. These survey responses are de-identified to protect participants' privacy. Staff participants indicate interest in a follow-up qualitative interview during the consent process. Verbal consent is obtained over the telephone before the start of the qualitative interview.

Participants

Clinic Staff

Clinic staff participants may include any staff, provider, or administrator employed at any of the three clinics in the phase 2 study. Across all three clinics, at each evaluation time point, there will be up to 100 staff surveys, 45 staff key informant interviews, and 20 staff focus group participants. Cross-sectional enrollment at each evaluation time point rather than a longitudinal assessment of select staff over the entire study period was selected given the staff turnover.

Clinic Patients

Patient participants include self-identified, female patients receiving care by a provider on the day of assessment at any of the three clinic sites. As the three clinics see women of varying ages, we will not restrict to younger ages. This will allow for a comprehensive assessment of PrEP implementation in these clinics, across their patient population, and identification of age-specific associated factors. Patient participants who complete the one-time patient exit survey must be aged 13 to 45 years, able to speak and understand English, not self-reported HIV positive, and have completed a visit at one of the three clinics on the day of survey consent. Patient exit surveys will occur approximately once quarterly for up to 9 time points (depending on onset of implementation phase), with up to 60 participants across all three clinics per time point. Patient participants may complete a survey at more than one time point, but their responses will not be linked.

Cohort Patients

Patient participants enrolled into the cohort component of this study must meet additional inclusion and exclusion criteria. These participants must have been seen for a patient visit in one of the three implementation clinics during the preceding 60 days and identified as a PrEP candidate based on HIV testing and risk assessment. In addition, they must not be currently enrolled in an HIV vaccine trial, have not been on PrEP for 7 or more consecutive days in the past, not be currently receiving PrEP care outside of the three clinics, and not be currently participating in another PrEP or candidate PrEP study. This cohort has a target enrollment of 300.

Recruitment

Clinic Staff

All clinic staff, including providers and administrators, who are part of FP services at each clinic site will be approached for participation by study staff. Clinic staff will be invited via email to participate in staff surveys. As part of the survey, individuals will be asked if they are interested in potentially participating in key informant interviews. Among those who indicate their willingness, a select group within each clinic will be purposefully selected and invited via email or phone to participate in key informant interviews. Finally, individuals comprising the Clinic Change Team, including the designated PrEP Champion, will be invited via email to participate in focus groups. Clinic leadership at each clinic site will select a PrEP Champion as well as a Clinic Change Team.

Clinic Patients

Clinic patient participants will be recruited by trained study staff. Specifically, study staff will attend clinic on days when FP patients are being seen and will review the daily FP clinic schedule with a designated FP clinic staff member to identify

individuals to approach for recruitment (see eligibility criteria). Study staff will approach potentially eligible patients and invite them to participate in the exit survey immediately following their provider visit.

Cohort Patients

Cohort patient participants will be recruited for the study using flyers and clinic staff referrals. Clinic staff will refer PrEP-eligible women who meet the eligibility criteria and agree to be contacted for a potential research study directly to study staff. In addition, clinic staff will distribute flyers to potential participants with study staff contact information, and study staff will be present in the clinics during regular intervals to facilitate on-site recruitment.

Incentives

All participants (clinic staff and patients) will be offered compensation for their time.

Data Collection

Clinic Staff

Aggregate of quarterly clinic-level data will be collected via clinic medical chart abstraction over the course of the study.

Quantitative and qualitative data will be collected for staff participants at three time points (approximately annually). Quantitative data will be collected via a web-based survey [31], taking approximately 20-30 min to complete. For the staff survey, the study staff will distribute the survey link via clinic email addresses. Qualitative data collection includes key informant interviews and focus groups. Key informant interviews will last approximately 60 min and will occur either in person or over the telephone. Staff participants who comprise the Clinic Change Team, which includes clinic staff and administrators who participated in PrEP implementation trainings and are involved in PrEP implementation in their clinics, will participate in in-person focus groups. Focus groups are expected to last 60-90 min. Trained study staff will conduct key informant interviews and focus groups, with at least two study staff facilitating focus groups (one as facilitator and one as a note taker). All interviews and focus groups will be audio recorded and sent for professional transcription.

Clinic Patients

Clinic patient participants will complete a brief (less than 10 min) interviewer-assisted patient exit survey following a visit at one of the three FP clinics. Clinic patient participants will be recruited approximately quarterly.

Cohort Patients

Data relevant to cohort patient participants will encompass medical chart review, interviewer-administered surveys, audio computer-assisted self-interviews, and pharmacologic and laboratory data. Data for cohort patient participants will be collected by trained study staff at the baseline, 3-month, and 6-month follow-up visits, with the allowance for interim visits as needed.

Quantitative Data Analysis

Sample Size

The prospective cohort study will attempt to enroll up to 300 PrEP-eligible women across three clinics. Sample sizes pertaining to clinic staff and clinic patient participants were not chosen to yield a specified level of statistical power for hypothesis testing or to provide a specific level of precision for estimation of a target estimand. However, based on a sample size of 300, the study will provide the ability to estimate the percentage of PrEP-eligible women who are willing to initiate PrEP at baseline within a margin of error of approximately 4.5% (assuming a true uptake percentage of 20%). If instead only 150 participants are enrolled, the margin of error increases to 6.4%. If the actual uptake is lower than assumed, the margin of error will be less than stated.

As this is the first study of its kind focusing on the components of the PrEP cascade in this population and estimates for uptake of PrEP are not available for women seeking care in FP clinics in the Southern United States, the distribution of patients who achieve each step of the PrEP cascade is not well understood. As a result, the quantitative data analysis objectives for the study are not powered for any specific hypothesis testing aim or to achieve a particular level of precision for a specific target estimand. However, based on a sample size of 300, the study will provide 70% power or more to detect a 12% difference in PrEP uptake between race groups (binary) provided the sample size distribution between the two race groups is not more imbalanced than 2:1, assuming a true uptake percentage in two groups of 15% and 27%, and based on a 5% significance level for the test.

Outcomes

The primary objectives of this study are to describe how implementation strategies affect the implementation of PrEP care in FP clinics, by analyzing clinic study data over time from pre- to post-PrEP implementation (Table 1), and to describe the PrEP cascade among women seeking care in FP clinics in Metro Atlanta (Table 2). The outcomes within the PrEP cascade include HIV testing, risk assessment, and prevention counseling inclusive of PrEP; PrEP prescriptions; and PrEP uptake, persistence, and adherence in PrEP-eligible women (Figure 2). As data capturing the entire span of the PrEP cascade and factors impacting successful implementation could not be captured by one data source, multiple data sources were necessary.

Table 1. Description of outcomes supporting the study's primary objective to describe how implementation strategies affect the implementation of HIV pre-exposure prophylaxis care in family planning clinics among women aged 13 to 45 years.

Outcomes	Definitions
Clinic staff (survey, focus groups, and key informant interviews)	
Implementation processes	Degree of adherence to the clinic-specific PrEP[a] implementation plans over assessment period
Factors affecting implementation	CFIR[b]-guided factors, assessed after PrEP implementation begins, that contribute to adherence to or deviations from the clinic-specific PrEP implementation plans
Clinic chart abstraction	
HIV testing	Change over time from pre- to post-PrEP implementation in the percentage of visits at the clinic in women aged 13 to 45 years where HIV testing was performed
HIV risk assessments	Change over time from pre- to post-PrEP implementation in the percentage of visits at the clinic in women aged 13 to 45 years with a documented HIV risk assessment
PrEP prescriptions	Change over time from pre- to post-PrEP implementation in the percentage of visits at the clinic in women aged 13 to 45 years at which a prescription for PrEP was received
Clinic patients (exit survey)	
HIV prevention counseling	Change over time from pre- to post-PrEP implementation in the percentage of clinic patient participants who report whether they received HIV prevention counseling during their visit to the clinic that day
HIV prevention counseling inclusive of information about PrEP	Change over time from pre- to post-PrEP implementation in the percentage of clinic patient participants who receive HIV prevention counseling that includes information about PrEP during their visit to the clinic that day

[a]PrEP: pre-exposure prophylaxis.

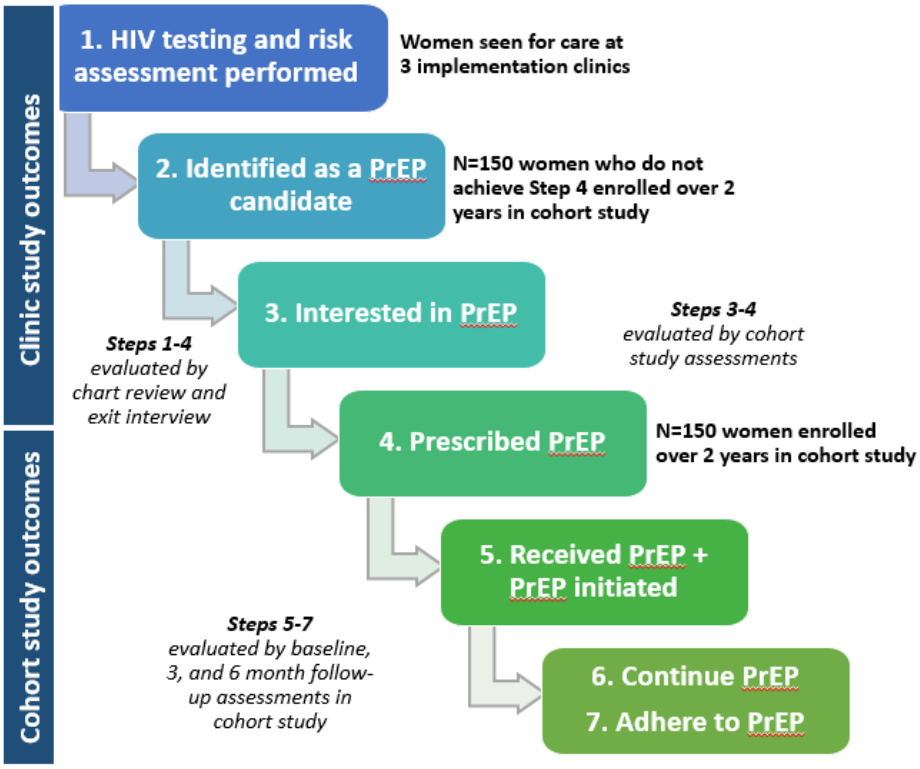
[b]CFIR: Consolidated Framework for Implementation Research.

Table 2. Description of outcomes supporting the study's primary objective to describe the HIV pre-exposure prophylaxis care cascade among women aged 13 to 45 years.

Outcomes	Definitions
Clinic chart abstraction	
HIV testing	Percentage of visits at the clinic in women aged 13 to 45 years where HIV testing was performed
HIV risk assessments	Percentage of visits at the clinic in women aged 13 to 45 years with a documented HIV risk assessment
PrEP[a] prescriptions	Percentage of visits at the clinic in women aged 13 to 45 years at which a prescription for PrEP was received
Clinic patients (exit survey)	
HIV prevention counseling	Percentage of clinic patient participants who report whether they received HIV prevention counseling during their visit to the clinic that day
HIV prevention counseling inclusive of information about PrEP	Percentage of clinic patient participants who receive HIV prevention counseling that includes information about PrEP during their visit to the clinic that day
Cohort patients	
PrEP uptake	Participant who receives a PrEP prescription at the baseline visit, fills their prescription, and self-reports initiating PrEP
PrEP persistence	Participant who attends at least one follow-up visit and has a documented pharmacy refill of PrEP medication at least once during each 3-month interval
PrEP adherence—hair sample	Average tenofovir concentration measured using a small hair sample (ng/mg); percentage of participants with adherence level consistent with 7 doses per week (≥0.0370 ng/mg) [34,35]
PrEP adherence—blood sample	Percentage of participants with dried blood spot tenofovir concentration≥1250 fmol/punch
PrEP adherence—urine sample	Percentage of participants with tenofovir detected by urine immunoassay
PrEP adherence—self-report	Percentage of participants reporting no missed doses in the past 7 days; percentage of participants reporting very good or excellent adherence (5 or 6 on a 6-level Likert scale) [36] in the past 30 days; percentage of participants who self-report adherence of 90% or higher
PrEP adherence—pharmacy fill	Percentage of participants with 80% adherence by medication possession ratio defined as the number of dispensed pills divided by the number of days since starting PrEP [37,38]

[a]PrEP: pre-exposure prophylaxis.

Figure 2. Overview of the study design and outcomes. PrEP: pre-exposure prophylaxis.



The clinic staff survey outcomes include the following CFIR domains to support a secondary objective of exploring provider and staff- and clinic-level factors and their association with steps in the PrEP care cascade. These steps include (1) inner setting readiness for implementation, (2) inner setting: implementation climate, (3) characteristics of individuals: knowledge and beliefs, (4) characteristics of individuals: self-efficacy, (5) characteristics of individuals: attitudes, (6) inner setting: leadership engagement, and (7) inner setting: available resources. These outcomes are more specifically defined in the protocol for phase 1 of this study [37].

Cohort patient outcomes to support a secondary objective specific to individual patient-level factors and their association with steps in the PrEP care cascade include comparing incidence of sexually transmitted infections, pregnancy, and HIV infection; contraception use; and contraception method adherence among the PrEP participants compared with the non-PrEP participants and characterizing PrEP interest, initiation, and indication, over time, for all participants.

Statistical Analysis

For quantitative outcomes defined based on chart abstraction (HIV testing, HIV risk assessments, and PrEP prescriptions) and clinic patient exit surveys (HIV prevention counseling, HIV prevention counseling including information about PrEP), we will compute the proportion of patients meeting the outcome definition (eg, portion who received an HIV test) along with 95% confidence intervals. For analyses based on clinic patient exit surveys, data from all exit surveys will be included in the statistical analysis.

For quantitative outcomes defined for cohort patients, all data will be included in analyses for all patients from enrollment until completion of the study or until the patient discontinues participation or becomes lost to follow-up. For the PrEP uptake and PrEP persistence outcomes, the proportion of patients meeting the outcome definition along with 95% confidence intervals will be computed. Association analyses will be performed using mixed logistic regression models to determine whether outcomes are associated with patient-level characteristics such as age, race, education level, and relationship status.

For PrEP adherence outcomes, data from all patients who initiate PrEP at their baseline visit will be included in the analyses. The proportion of patients meeting each PrEP adherence outcome definition along with 95% confidence intervals will be computed at the 3- and 6-month post baseline time points. Analyses will be performed using mixed logistic regression models to determine whether adherence outcomes are associated with patient-level characteristics such as age, race, education level, and relationship status and whether adherence rates change over the 6-month observation period. Analyses will be performed that also incorporate data from patients who initiate PrEP after their baseline visit. Agreement between the different PrEP adherence outcome measures will also be assessed using standard methods (eg, weighted kappa statistic).

Before the analysis of quantitative data, a comprehensive statistical analysis plan will be developed and finalized. Primary and secondary study outcomes and statistical analysis methods will be described in full detail in the study's statistical analysis plan. This plan will be accessible on ClinicalTrials.gov once available.

Qualitative Data Analysis

Coding of the key informant interview and focus group data will follow a content analysis and deductive approach, using the CFIR. Analysts will remain open to new themes that may arise inductively from the data. The coding process will follow a consensual research approach, where multiple judges are used throughout the data analysis to ensure multiple perspectives. Then, consensual validation is achieved through a process of deliberation and consensus among judges, and then, an individual *external* to the team (an outside qualitative expert) will review the process to maximize the validity of the findings. After the codebook is finalized, the qualitative coding will be conducted in 3 phases: (1) organize data with codes and build a foundation for case-based analysis (each clinic is considered a case); (2) using NVivo 11 (QSR International), a pair of analysts will code transcripts and meet to reach consensus, and then, final codes will be applied for each transcript; and (3) pairs of analysts will draft a case memo, organized by constructs. The case will be developed iteratively as each transcript is coded, added to, and used to refine the memo. Rigor for qualitative research will be employed by having verbatim transcripts, structured codebook and coding training, double coding, and team consensus on data themes.

Integration and Dissemination of Findings

For objective one addressing clinic-level factors related to PrEP adoption and implementation, clinic study primary outcomes (Table 2; chart abstraction and clinic patient outcomes), clinic staff survey secondary outcomes (CFIR domains), and data themes from staff interviews and focus group data will be summarized overall and for each of the three FP clinics. For objective two evaluating the effect of PrEP integration in FP clinics on PrEP uptake, persistence, and adherence, each step in the PrEP cascade and its associated factors will be summarized. Findings will be disseminated to key stakeholders, including the three participating FP clinics.

Results

Research activities for this study began in February 2018 and are ongoing. As of March 08, 2020, all three clinics have begun providing PrEP, and 120 clinic patient exit surveys, 1 focus group with 4 participants, 1 key informant interview, and 13 cohort patient baseline visits have been completed. Qualitative data analysis is scheduled to begin in Fall 2020.

Discussion

Although FP clinics may be an ideal setting for PrEP delivery, there is a lack of available data from health care providers, administrators, and patients to guide optimal integration of PrEP into various safety net clinical settings, particularly for women's health care settings [39,40]. By simultaneously evaluating multilevel factors associated with the level of PrEP adoption and implementation and the effects of PrEP implementation on PrEP uptake, persistence, and adherence among women over a 6-month follow-up period, this study will provide an abundance of meaningful data to further guide PrEP integration in Title X–funded clinics across the Southern United States.

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Conflicts of Interest

JMS and ANS received grants from Gilead Sciences in the last 3 years.

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Abbreviations

ATN: Adolescent Medicine Trials Network for HIV/AIDS Interventions
AYAW: adolescent and young adult women
CFIR: Consolidated Framework for Implementation Research
EPIS: Exploration, Preparation, Implementation, and Sustainment
FP: family planning
IRB: institutional review board
PrEP: pre-exposure prophylaxis

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